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Research: Complications

Glycaemic control and risk of incident urinary incontinence in women with Type 1 diabetes: results from the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC)

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What's new?

- Research to date has failed to show an association between glycaemic control and urinary incontinence (UI) in women with diabetes.
- We examined the relationship between HbA_{1c} and UI using longitudinal data from the Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study.
- Our findings show that the odds of UI increase with poor glycaemic control in women with Type 1 diabetes, independently of other well-described predictors of UI.

Abstract

Aims To study the impact of glycaemic control on urinary incontinence in women who participated in the Diabetes Control and Complications Trial (DCCT; 1983–1993) and its observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC; 1994–present).

Methods Study participants were women who completed, at both years 10 (2003) and 17 (2010) of the EDIC follow-up, the urological assessment questionnaire (UroEDIC). Urinary incontinence was defined as self-reported involuntary leakage of urine that occurred at least weekly. Incident urinary incontinence was defined as weekly urinary incontinence present at EDIC year 17 but not at EDIC year 10. Multivariable regression models were used to examine the association of incident urinary incontinence with comorbid prevalent conditions and glycaemic control (mean HbA_{1c} over the first 10 years of EDIC).

Results A total of 64 (15.3%) women with Type 1 diabetes (mean age 43.6 ± 6.3 years at EDIC year 10) reported incident urinary incontinence at EDIC year 17. When adjusted for clinical covariates (including age, DCCT cohort assignment, DCCT treatment arm, BMI, insulin dosage, parity, hysterectomy, autonomic neuropathy and urinary tract infection in the last year), the mean EDIC HbA_{1c} was associated with increased odds of incident urinary incontinence (odds ratio 1.03, 95% CI 1.01–1.06 per mmol/mol increase; odds ratio 1.41, 95% CI 1.07–1.89 per % HbA_{1c} increase).

Conclusions Incident urinary incontinence was associated with higher HbA_{1c} levels in women with Type 1 diabetes, independent of other recognized risk factors. These results suggest the potential for women to modify their risk of urinary incontinence with improved glycaemic control.

(Clinical Trials Registry no: NCT00360815 and NCT00360893).

Introduction

Urinary incontinence (UI), or the complaint of involuntary leakage of urine, is one of the most prevalent chronic conditions in women. Although the estimated prevalence of UI varies depending on the definition applied and the age range of the population under study, on average 20–25% of women aged 40–50 years report having UI, leading to significant distress and reduced quality of life [1]. Epidemiological studies suggest that diabetes is an independent risk factor for UI in women [2,3]. The evidence regarding the effect of poor glycaemic control on subsequent UI among women with diabetes, however, is limited and unclear. It has been hypothesized that poor glycaemic control could contribute to this problem, either acutely by causing glycosuria, or chronically, by causing neuropathy [4,5]; however, recent studies have failed to show an association between glycaemic control and UI in women with diabetes [6–9]. The studies were limited by their cross-sectional design, inclusion of women primarily with Type 2 diabetes and relatively small sample of women with poor glycaemic control.

The objective of the present study was to determine whether long-term mean HbA_{1c} levels among women with Type 1 diabetes were associated with UI development after accounting for established risk factors. We hypothesized that poor glycaemic control in Type 1 diabetes may result in an increased risk of UI. We examined the relationship between HbA_{1c} levels and UI

using data from the Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. The DCCT/EDIC study has collected detailed information on subjects with Type 1 diabetes since 1983. Information regarding UI has been collected since 2003 in an ancillary study of urological complications of diabetes (UroEDIC). **Patients and methods**

Population and setting

The DCCT was a multicentre, randomized clinical trial designed to compare the effects of intensive and conventional diabetes therapy on the development and progression of early microvascular and neuropathic complications of Type 1 diabetes [10]. From 1983 to 1989, 1441 patients (including 680 women) aged 13–39 years were recruited at 29 centres. The DCCT included a primary prevention cohort and a secondary intervention cohort. The primary prevention cohort included 348 women with a diabetes duration of 1–5 years at baseline, no retinopathy and a urinary albumin excretion rate <40 mg/24 h. The secondary intervention cohort included 332 women with diabetes duration of 1–15 years at baseline, non-proliferative retinopathy and a urinary albumin excretion rate ≤ 200 mg/24 h. Individuals were excluded if they had hypertension, a history of symptomatic ischaemic heart disease, or the presence of symptomatic peripheral neuropathy requiring therapy. The intensive-therapy regimen was designed to achieve glycaemic control as close to the non-diabetes range as safely possible with ≥ 3 daily insulin injections or by use of an insulin pump, with insulin dose adjustment guided by frequent self-monitoring of blood glucose. Conventional therapy consisted of 1–2 daily insulin injections without prespecified target glucose levels and aimed for absence of symptomatic hyperglycaemia or frequent or severe hypoglycaemia. At the end of the trial in 1993, after a mean follow-up of 6.5 years, the DCCT proved that intensive therapy significantly reduced the risks of microvascular complications compared with conventional treatment [11]. Intensive treatment was subsequently encouraged for all subjects, who then returned to their own healthcare providers for ongoing diabetes care.

In 1994, 655 (96%) of the 680 surviving women (mean age 35 ± 7 years), volunteered to participate in the EDIC study. During EDIC year 10 (2003–2004), 550 of the 652 active female participants (84%), agreed to participate in the UroEDIC study, an ancillary study to examine the presence of urological complications, including UI, lower urinary tract symptoms, urinary tract

infections and sexual dysfunction. In EDIC year 17 (2010–2011), 580 of the 618 active female participants (94%), completed the UroEDIC protocol. A total of 500 women (mean age 51 ± 7 years), provided information on UI at both EDIC years 10 and 17. Of these 500 women, 417 did not report UI at EDIC year 10 and were eligible for the study of incident UI at EDIC year 17 (Fig. 1). The institutional review board of each participating centre approved the study.

Measurement of urinary incontinence

Assessment of UI was performed at EDIC years 10 and 17 with a self-administered questionnaire using validated instruments from previous studies [12]. The sequence of incontinence questions began with, 'During the past 12 months how often have you leaked even a small amount of urine...'. The frequency of incontinence was ascertained as every day, ≥ 1 time weekly, ≥ 1 time monthly, or < 1 time per month. The primary outcome of interest was weekly or more frequent UI, which we defined as 'weekly UI'. Those subjects with less than weekly or no UI were defined as having 'no UI'. Among women with weekly UI, the type of incontinence during the past 7 days was classified by answers to the additional questions, '...during activities such as coughing, sneezing, lifting or exercise?' (stress incontinence) and '...with an urge to urinate and could not get to the bathroom fast enough?' (urge incontinence). Those who reported both types were placed in the category 'mixed incontinence'. Incident UI was defined by cases of weekly UI present at EDIC year 17 but not at EDIC year 10. Urinary tract infection was also assessed at EDIC years 10 and 17 by self-report with the following question, 'How many times were you diagnosed by a physician with a bladder infection in the previous 12 months?'. For the purposes of the present study, urinary tract infection at EDIC year 17 was defined as ≥ 1 episode in the past 12 months.

Diabetes measurements

Each participant in the EDIC study underwent an annual medical history, physical examination and laboratory testing including HbA_{1c}, using the same methods as those used during the DCCT [13]. HbA_{1c} levels were measured at baseline and quarterly during the DCCT, and annually in the EDIC study using high-performance ion-exchange liquid chromatography, as previously described [14]. For the purposes of the present analysis, we used the mean HbA_{1c} during EDIC years 1–10 as the exposure variable. This time frame was chosen to ensure temporality of the

HbA_{1c} and UI relationship, as annual UI development was not available between the years 10 and 17. Retinopathy was assessed using fundus photographs that were centrally graded using the Early Treatment Diabetic Retinopathy Study scale. The albumin excretion rate was measured in half of the cohort annually. Nephropathy was defined as an albumin excretion rate >30 mg/24h. Peripheral neuropathy was defined by the Michigan Neuropathy Screening Instrument as >6 responses on the questionnaire or a score of >2 on the examination. Abnormal cardiovascular autonomic neuropathy was defined as: either R-R variation <15 or R-R variation between 15 and 19.9, plus either a Valsalva ratio ≤1.5 or a supine-to-standing drop of ≥ 10 mm Hg in diastolic blood pressure.

Statistical analysis

The distribution of demographic and clinical characteristics, cohort and treatment, markers of diabetes control and microvascular complications at EDIC year 10 were compared according to incident weekly UI status at EDIC year 17 using the chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. A multivariable logistic regression model was used to estimate the association between glycaemic control (mean HbA_{1c} from EDIC year 1 to year 10) and incident weekly UI at EDIC year 17. Adjustments for *a priori* predictors of UI described in the literature and those that were significant in bivariate analyses were performed. The following EDIC year 10 adjustment variables were used for multivariable models: age; DCCT cohort assignment; DCCT treatment arm; EDIC mean BMI; total daily insulin dosage; parity; hysterectomy; autonomic neuropathy; and urinary tract infection in the last year. Effects nominally significant at $P \leq 0.05$ are reported. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Among the 417 women who did not report at least weekly UI at EDIC year 10, 64 reported at least weekly UI at EDIC year 17 representing an incidence of weekly UI of 15.3% over this 7-year time frame. These women were classified as having either mixed UI ($n=29$, 45.3%), stress UI ($n=27$, 42.2%) or urge UI ($n=5$, 7.8%). Type of UI was not specified by three (4.7%) women. There were no significant differences in the characteristics of women with and without UI at EDIC year 10 with respect to age, race, parity, menopausal status, hysterectomy or urinary tract

infection within the past year (Table 1). Mean BMI at EDIC year 10 was greater in women reporting incident UI compared with women reporting less frequent UI ($P=0.08$). Intensive vs conventional therapy assignment during DCCT was associated with incident weekly UI during the EDIC study ($P=0.03$), with a higher frequency of incident UI in women assigned to intensive therapy during the DCCT. The DCCT cohort (primary vs secondary) was not associated with incident weekly UI ($P=0.79$).

Women with incident weekly UI had higher mean HbA_{1c} levels at EDIC year 1 [68 ± 16 mmol/mol ($8.3 \pm 1.5\%$) vs 62 ± 14 mmol/mol ($7.8 \pm 1.3\%$); $P=0.01$] and EDIC year 10 [68 ± 15 mmol/mol ($8.4 \pm 1.4\%$) vs 61 ± 14 mmol/mol ($7.8 \pm 1.2\%$); $P=0.001$] as compared with women who did not develop UI by EDIC year 17. Similarly, mean HbA_{1c} up to EDIC year 10 was higher in women with incident weekly UI compared with women who did not develop UI between EDIC years 10 and 17 [68 ± 14 mmol/mol ($8.4 \pm 1.2\%$) vs 63 ± 12 mmol/mol ($7.9 \pm 1.1\%$); $P=0.003$]. Women with weekly UI also reported a higher mean daily dose of insulin during EDIC years 1–10 (0.59 ± 0.16 vs 0.55 ± 0.17 units/kg/day; $P=0.03$). The frequency of diabetes-associated microvascular complications, such as proliferative retinopathy, nephropathy, peripheral neuropathy and autonomic neuropathy, did not differ between women with and without incident weekly UI (Table 1).

A multivariable logistic regression model was used to estimate the association between unit changes in glycaemic control and incident weekly UI after adjustment for age, DCCT treatment group, DCCT cohort assignment, BMI, EDIC mean daily insulin dose, parity, hysterectomy, autonomic neuropathy and UTI (Table 2). Long-term poor glycaemic control, as defined by higher mean HbA_{1c} levels in EDIC years 1–10 was associated with an increased risk of UI (odds ratio 1.03, 95% CI 1.01–1.06 per mmol/mol increase in HbA_{1c}; odds ratio 1.41, 95% CI 1.07–1.89 per % increase in HbA_{1c}). Age, DCCT cohort assignment, DCCT treatment arm, BMI, EDIC mean insulin dosage, parity, hysterectomy, autonomic neuropathy and UTI in the last year were not significantly associated with incident UI independently of HbA_{1c}. Additional analysis examining tertile distribution of HbA_{1c} showed an increasing risk of UI with increasing HbA_{1c} levels. Women with EDIC mean HbA_{1c} levels in the second tertile [58 – 67 mmol/mol (7.42 – 8.25%)] had a 1.44 greater odds of UI, while those with levels in the highest tertile [≥ 67

mmol/mol (8.25%)] had a 2.50 greater odds of developing UI compared with women with HbA_{1c} levels <58 mmol/mol (7.42%; Fig. 2).

Discussion

The present study is the first to show the impact of glycaemic control on risk of UI among women with Type 1 diabetes. After adjustment for previously well-described risk factors, we observed a 3 and 41% increased odds of incident weekly UI associated with each 1-mmol/mol and 1% increase in HbA_{1c} level, respectively, in women with Type 1 diabetes. This association was independent of age, DCCT cohort assignment, DCCT treatment arm, BMI, insulin dosage, parity, hysterectomy, abnormal cardiovascular autonomic neuropathy and UTI in the last year. These data suggest that long-term glycaemic control may independently affect the development of UI in this population.

In contrast to the findings of the present study, previous studies have failed to identify an association between level of glycaemic control and UI [6–9]. In a study of women aged 55–75 years, enrolled in a group health plan, Jackson *et al.* [15] found no associations between HbA_{1c} (categorized as ≤7.5%, 7.6–8.5% and >8.5%) and UI. Similarly, Phelan *et al.* [7] did not observe a relationship between HbA_{1c} and UI among 2994 overweight/obese women with diabetes. Previous work in this cohort at EDIC year 10 also did not find an association between HbA_{1c} levels and prevalent UI [16,17]. There are several possible explanations for the discrepant findings between previous studies and the present results. First, the earlier studies included women almost exclusively with Type 2 diabetes and were limited in their cross-sectional designs. Second, these studies used measurement of HbA_{1c} at a single time point, a measure of current control (average glycaemic control over a period of a several months), while we used a measure of average glycaemic control over years of diabetes. Third, the average BMI in several of these studies was >35 kg/m² and it is possible that the greater weight may have impaired the detection of the effects of these measures on UI. Interestingly in a recent report of the Diabetes and Aging Study, a sample of women with Type 1 and 2 diabetes enrolled in the Kaiser Permanente Northern California Diabetes Registry, HbA_{1c} level was not associated with presence or absence of UI, but poor glycaemic control, defined as HbA_{1c} ≥9%, was associated with more limitations in daily activities as a result of UI [6]. This is consistent with the present

findings that the largest impact of glycaemic control on incident UI was among those with the highest tertile of HbA_{1c} levels [$>67\text{mmol/mol}$ (8.25%)].

The present findings showing that poor glycaemic control is associated with UI in patients with long duration of Type 1 diabetes is consistent with effects found with other diabetes complications. Microvascular and neurological complications of Type 1 diabetes, which are established pathological consequences of poor glycaemic control [11,18,19], result in changes that might damage innervation of the bladder or alter bladder muscle function, which may precipitate or worsen urinary symptoms [4,5,20,21]. Hyperglycaemia also causes increased glucosuria and urine volume, which could be a contributing factor. Improving glycaemic control has been advocated as a means of improving urinary symptoms [22].

Interestingly, we observed that those women initially randomized during the DCCT to the intensive treatment arm (as opposed to conventional treatment) have a higher incidence of weekly UI in bivariate analyses. It is possible that this is related to increased insulin exposure in the intensive treatment group, resulting in insulin-related weight gain [23,24] which could cause increased intra-abdominal pressure and lead to increased bladder pressure and urethral mobility [25,26]. Notably, after multivariable model adjustment for mean insulin dose and BMI during the EDIC interval, the effect of randomization to intensive treatment on UI risk was no longer statistically significant. Further studies examining the complex relationship between insulin dose and effects on body size are necessary.

There are several important clinical implications for the present findings. First, the 7-year incidence (15.3%) of weekly UI in the present study is lower than that observed for other populations [27,28]. While this could be a function of the variation in the definition of UI across studies, it is also possible that this is a result of improved glycaemic control, which may have contributed to the prevention of symptoms. We cannot exclude the additional possibility that women with Type 1 diabetes may be less likely to report or discuss urinary symptoms [29]. Second, for women with Type 1 diabetes our data suggest that improved glycaemic control may decrease the risk of incident UI. These findings provide a compelling argument for the routine assessment and counselling for UI in women with Type 1 diabetes. Offering women the knowledge that they can potentially decrease their risk of UI with improved glycaemic control

might motivate some women to improve their self-care. This may be especially important given traditional treatments for UI have been found to be less effective in women with diabetes [30].

The present study is the largest examination of the impact of glycaemic control on UI in the literature among women with Type 1 diabetes. Its strengths include the minimal loss to follow-up and frequent validated measurement of key covariates. The long duration of follow-up allowed the exploration of long-term glycaemic control and BMI, and their relative impact on UI risk. The study also has several limitations. While the cohort has been followed for many years, participants are still relatively young and almost all are white. Also, DCCT/EDIC participants are generally a highly motivated group of individuals who have been followed for many years with a goal of good diabetes control, so these results may not apply to a broader population with Type 1 diabetes. Further, it is unclear whether these results extend to women with Type 2 diabetes, who generally have a different demographic profile from women with Type 1 diabetes, and have a later age of diabetes onset and a higher prevalence of obesity. Finally, we were unable to evaluate the impact of glycaemic control on specific types of UI because of the limited sample size and power. Further longitudinal follow-up of this cohort should enable these events to be examined.

In conclusion, the present findings show that the odds of UI increase with poor glycaemic control in women with Type 1 diabetes. This relationship is independent of other well-described predictors of UI and suggests that factors directly related to glycaemic control may be affecting urinary symptoms. Offering women the knowledge that they can potentially decrease their risk of UI with aggressive glycaemic control might motivate women to more strictly adhere to glycaemic therapies to reduce other more serious risks of diabetes sequelae.

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Competing interests

None declared.

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FIGURE 1 Flow of participants in the DCCT/EDIC/UroEDIC study. DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications study; UroEDIC, EDIC substudy on urological complications; UI, urinary incontinence.

FIGURE 2 Multivariable adjusted odds ratios of incident weekly urinary incontinence (UI) at Epidemiology of Diabetes Interventions and Complications study (EDIC) year 17 by tertiles of HbA_{1c} (EDIC mean HbA_{1c} up to year 10 [HbA_{1c} reference <58 mmol/mol or <7.38%]). *P* value based on overall Wald chi-squared test for parameter estimate of HbA_{1c} in the multivariable logistic regression model shown in Table 2. Odds of incident weekly UI at EDIC year 17 adjusted for the following EDIC year 10 characteristics: attained age; Diabetes Control and Complications Trial (DCCT) cohort assignment; DCCT treatment group; EDIC mean daily insulin dose; EDIC mean BMI; parity; hysterectomy; autonomic neuropathy; and urinary tract infection.

Table 1. Participant characteristics at EDIC year 10 by incident weekly urinary incontinence status at EDIC year 17

	No UI or less than weekly UI (n=353)	Weekly UI (n=64)	<i>P</i> *
Sociodemographic and clinical characteristics			
Mean (SD) attained age (years)	43.1±7.4	43.6±6.3	0.69
Smoker†, <i>n</i> (%)	49 (14)	8 (13)	0.77
Drinker†, <i>n</i> (%)	125 (35)	23 (36)	0.94
Race, <i>n</i> (%)			
Non-Hispanic white	343 (97)	63 (98)	0.53
Non-Hispanic black	7 (2)	0 (0)	
Other	3 (1)	1 (2)	
Parity (<i>n</i> of live births), <i>n</i> (%)			
0	106 (30)	16 (25)	0.53
1	64 (18)	15 (23)	
≥2	183 (52)	33 (52)	
Hysterectomy‡, <i>n</i> (%)	35 (10)	3 (7)	0.17
Postmenopausal, <i>n</i> (%)	86 (25)	12 (19)	0.28
Mean (SD) BMI, kg/m ²			

EDIC mean up to year 10	26.3±4.1	27.4±4.5	0.08
EDIC year 10	27.0±4.8	27.8±5.1	0.27
Mean (SD) BMI gain during EDIC, kg/m ²	1.4±3.1	1.4±3.1	0.48
Urinary tract infection (within past year) [§] , <i>n</i> (%)	52 (15)	12 (19)	0.44
Diabetes control and treatment			
DCCT cohort, <i>n</i> (% primary prevention)	183 (52)	32 (50)	0.79
Treatment group, <i>n</i> (% intensive)	178 (50)	42 (66)	0.03
Mean (SD) HbA _{1c} , mmol/mol			
EDIC year 1	62±14	68±16	0.01
EDIC year 10	61±14	68±15	0.001
EDIC mean up to year 10	63±12	68±14	0.003
Mean (SD) HbA _{1c} , %			
EDIC year 1	7.8±1.3	8.3±1.5	0.01
EDIC year 10	7.8±1.2	8.4±1.4	0.001
EDIC mean up to year 10	7.9±1.1	8.4±1.2	0.003
Mean (SD) insulin dose, units/kg/day			
EDIC year 10	0.60±0.23	0.69±0.25	0.003
EDIC mean up to year 10	0.55±0.17	0.59±0.16	0.03
Microvascular complications			
Retinopathy [¶] , <i>n</i> (%)	50 (15)	10 (16)	0.82
Nephropathy [¶] , <i>n</i> (%)	43 (13)	5 (8)	0.30
Peripheral neuropathy ^{**} , <i>n</i> (%)	102 (29)	22 (34)	0.38
Autonomic Neuropathy ^{††} , <i>n</i> (%)	98 (30)	23 (37)	0.25

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications study.

**P* values based on the Wilcoxon rank-sum test for quantitative characteristics or the contingency chi-squared test for qualitative characteristics.

†Smoking was defined as 'currently smokes cigarettes or ever smoked in the past 12 months (any amount)'. Drinking was defined as 'consumed an average of at least one alcoholic beverage per week during the past 12 months'

‡Hysterectomy defined by report of surgically induced menopause.

§Urinary tract infection was determined at EDIC year 10 by self-report with the following question, 'How many times were you diagnosed by a physician with a 'bladder infection' in the previous 12 months?'. Urinary tract infection was defined as ≥1 episode in past 12 months.

¶Defined up to EDIC year 10 using the Early Treatment Diabetic Retinopathy Study on a scale of 0–23. Proliferative diabetic retinopathy is defined as ≥12 and/or scatter or focal laser.

¶¶ Defined at EDIC year 9/10 as albumin excretion rate (mg/24h) >30.

** Defined at EDIC year 10 by the Michigan Neuropathy Screening Instrument >6 responses on the questionnaire or a score of >2 on the examination.

†† Defined at EDIC year 13/14 as R-R variation <15 or RR variation <20 in combination with a Valsalva ratio ≤ 1.5 or a decrease of >10 mm Hg in diastolic blood pressure upon standing.

Table 2 Adjusted multivariable logistic regression model examining the effect of glycaemic exposure on incident weekly urinary incontinence status at EDIC year 17

Risk factors at EDIC year 10	Odds ratio (95% CI)	P
Attained age (per year)	1.02 (0.97, 1.06)	0.53
DCCT cohort (primary prevention vs secondary intervention)	0.90 (0.50, 1.64)	0.74
DCCT treatment group (intensive vs conventional)	1.71 (0.92, 3.19)	0.09
EDIC mean BMI up to year 10 (kg/m ²)	1.05 (0.97, 1.12)	0.21
EDIC mean insulin dose up to year 10 (units/kg/day)	3.01 (0.50, 18.22)	0.23
Parity (<i>n</i> of live births)		
1 vs 0	1.79 (0.75, 4.27)	0.23
≥ 2 vs 0	1.33 (0.63, 2.83)	0.99
Hysterectomy (yes vs no)	0.31 (0.08, 1.21)	0.09
Autonomic neuropathy (yes vs no)	1.03 (0.51, 2.08)	0.93
Urinary tract infection (within past year) (yes vs no)	1.34 (0.62, 2.91)	0.46
EDIC mean HbA _{1c} up to year 10 (mmol/mol)	1.03 (1.01, 1.06)	0.02
EDIC mean HbA _{1c} up to year 10 (%)	1.41 (1.07, 1.89)	0.02

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications study.

Table 1. Participant Characteristics at EDIC year 10 by incident weekly UI status at EDIC year 17

	No UI or less than weekly UI (n=353)	Weekly UI (n=64)	p-value*
Sociodemographic and clinical			
Attained age (years) Mean (SD)	43.1±7.4	43.6±6.3	0.69
Smoker No. (%) †	49 (14)	8 (13)	0.77
Drinker No. (%) †	125 (35)	23 (36)	0.94
Race No. (%)			
Non-Hispanic White	343 (97)	63 (98)	0.53
Non-Hispanic Black	7 (2)	0 (0)	
Other	3 (1)	1 (2)	
Parity (n of live births) No. (%)			
0	106 (30)	16 (25)	0.53
1	64 (18)	15 (23)	
≥2	183 (52)	33 (52)	
Hysterectomy No. (%) ‡	35 (10)	3 (7)	0.17
Postmenopausal No. (%)	86 (25)	12 (19)	0.28
BMI (kg/m ²) Mean (SD)			
EDIC Mean through Year 10	26.3±4.1	27.4±4.5	0.08
EDIC Year 10	27.0±4.8	27.8±5.1	0.27
BMI Gain during EDIC (kg/m ²) Mean (SD)	1.4±3.1	1.4±3.1	0.48
UTI (within past year) No. (%) §	52 (15)	12 (19)	0.44
Diabetes control and treatment			
DCCT cohort No. (% primary prevention)	183 (52)	32 (50)	0.79
Treatment group No. (% intensive)	178 (50)	42 (66)	0.03
Hemoglobin A1c (mmol/mol) Mean (SD)			
EDIC Year 1	62±14	68±16	0.01
EDIC Year 10	61±14	68±15	0.001
EDIC Mean through Year 10	63±12	68±14	0.003
Hemoglobin A1c (%) Mean (SD)			
EDIC Year 1	7.8±1.3	8.3±1.5	0.01
EDIC Year 10	7.8±1.2	8.4±1.4	0.001
EDIC Mean through Year 10	7.9±1.1	8.4±1.2	0.003
Insulin Dose (units/kg/day), Mean (SD)			
EDIC Year 10	0.60±0.23	0.69±0.25	0.003

EDIC Mean through Year 10	0.55±0.17	0.59±0.16	0.03
Microvascular complications			
Retinopathy No. (%)	50 (15)	10 (16)	0.82
Nephropathy No. (%) ^{¶¶}	43 (13)	5 (8)	0.30
Peripheral Neuropathy No. (%) [#]	102 (29)	22 (34)	0.38
Autonomic Neuropathy No. (%) ^{**}	98 (30)	23 (37)	0.25

* P-values based on the Wilcoxon rank-sum test for quantitative characteristics or the contingency chi-square test for qualitative characteristics.

† Smoking is defined as "currently smokes cigarettes or ever smoked in the past 12 months (any amount)." Drinking is defined as "consumed an average of at least one alcoholic beverage per week during the past 12 months."

‡ Hysterectomy defined by report of surgically induced menopause.

§ Urinary tract infection (UTI) was determined at EDIC year 10 by self-report with the following question "how many times were you diagnosed by a physician with a "bladder infection" in the previous 12 months?" UTI defined as ≥1 episode in past 12 months.

^{||} Defined through EDIC year 10 using the Early Treatment Diabetic Retinopathy Study on a scale of 0-23. Proliferative diabetic retinopathy is defined as ≥12 and/or scatter or focal laser.

^{¶¶} Defined at EDIC year 9/10 as Albumin Excretion Rate (mg/24hr) >30.

[#] Defined at EDIC year 10 by the Michigan Neuropathy Screening Instrument >6 responses on the questionnaire or a score of >2 on the exam.

^{**} Defined at EDIC year 13/14 as R-R variation <15 or RR variation <20 in combination with a Valsalva ratio ≤1.5 or a decrease of >10 mm Hg in diastolic BP upon standing.

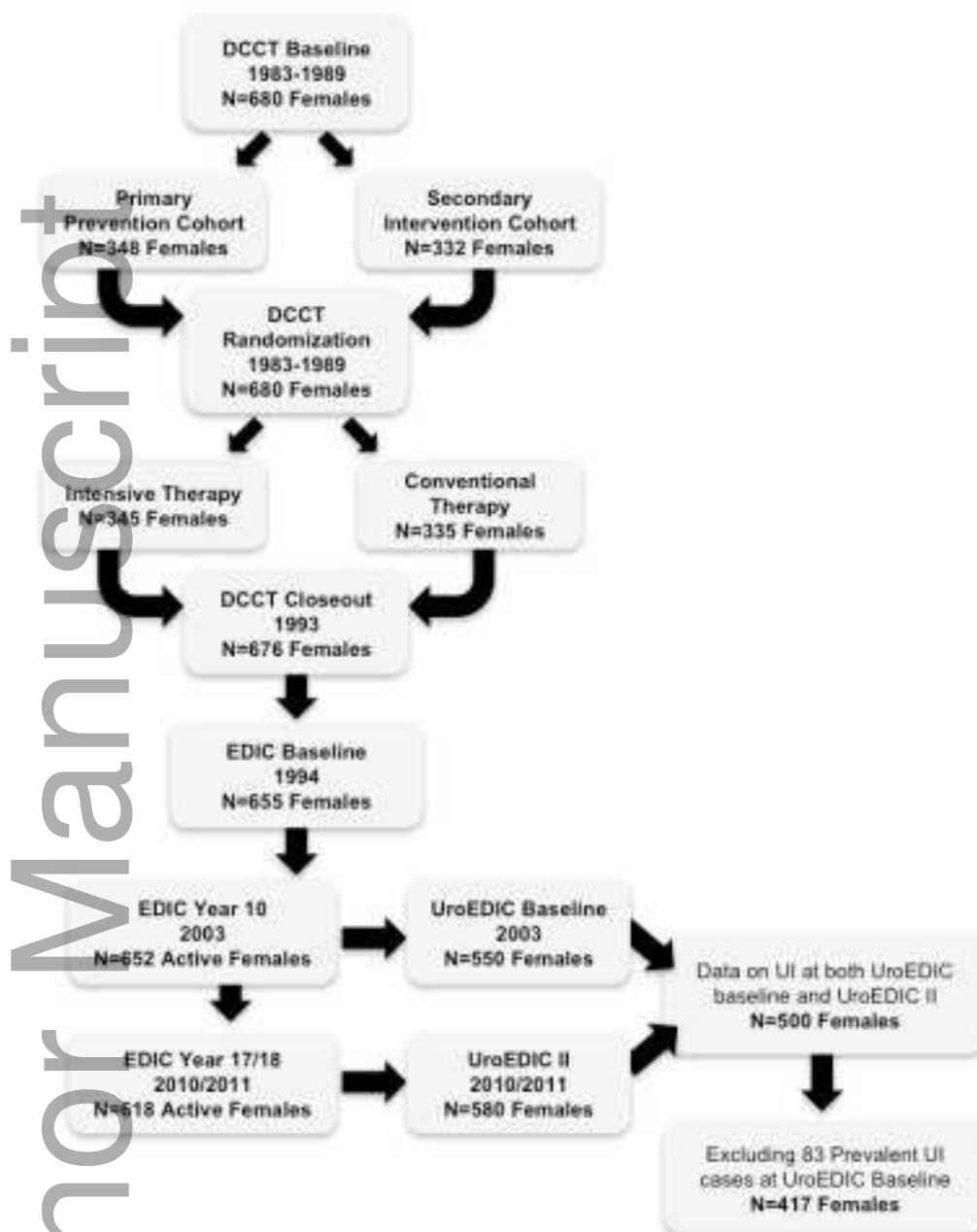
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Table 2. Adjusted multivariable logistic regression model examining the effect of glycemic exposure on incident weekly UI status at EDIC year 17

Risk Factors at EDIC Year 10	OR (95% CI)	p-value
Attained age (per year)	1.02 (0.97, 1.06)	0.53
DCCT cohort (primary prevention vs. secondary intervention)	0.90 (0.50, 1.64)	0.74
DCCT treatment group (intensive vs. conventional)	1.71 (0.92, 3.19)	0.09
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EDIC mean Insulin Dose through Year 10 (units/kg/day)	3.01 (0.50, 18.22)	0.23
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1 vs. 0	1.79 (0.75, 4.27)	0.23
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UTI (within past year) (yes vs. no)	1.34 (0.62, 2.91)	0.46
EDIC mean HbA1c through Year 10 (mmol/mol)	1.03 (1.01, 1.06)	0.02
EDIC mean HbA1c through Year 10 (%)	1.41 (1.07, 1.89)	0.02

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Figure 1. Flow of female participants in DCCT/EDIC/UroEDIC



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