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Dataset Integrity Check
EDIC 8-year Neuropathy Analysis Dataset

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March 18, 2007

As a partial check of the integrity of the Neuropathy Analysis dataset archived in the NIDDK data repository, a number of analyses were performed to duplicate results published by Martin et al. in *Diabetes Care* in 2006.[1] Appendix A presents the full text of this article. Appendix B presents a comparison of the DCC's report on distributions of study variables to calculations made from the archived dataset, and Appendix C contains SAS code for the tabulations and analyses reported in this text and Appendix B.

The intent of this integrity check is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is ***not*** to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected on a first (or second) exercise in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study DCC, however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is observed in an integrity check. Thus, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses unless staff of the NIDDK Repository suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff. We do, however, document (often in footnotes) those instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication.

DCC SUMMARY STATISTICS.

The DCC for EDIC supplied summary statistics (Ns, percents, means, etc.) for the variables included in the analysis file. Appendix B includes the statistics provided by the DCC and three additional columns containing the values obtained in our dataset integrity check. Our analysis largely replicated these statistics[2] --- with the exception of the handling of MSNI missing values.[3] The DCC has informed us that this apparent discrepancy reflects their purposeful recoding of missing data codes to values of zero.

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[1] Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, Stevens MJ, Feldman EL; DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care.* 2006 Feb;29(2):340-4.

[2] In addition to the handling of missing values described in Appendix D, the PT_Score variable in the archived dataset had 2,229 cases with a score of "3" (vs. 2,228 in DCC dataset documentation) and 298 cases with a score of "6" (vs. 297 in DCC dataset documentation).

[3] Across subjects and years of EDIC, we found 19 instances in which the *MSNI Checklist Score* (PT_SCORE) is coded as missing (.) but the binary indicator variable for "High" scores (PT_HIGH) is coded as zero ("not high", i.e., less than 7). Similarly, *MSNI Neuropathy Examination Scores* were calculated from 8 individual measurements made during the examination (EOCAL, EOCAR, EOC2L, EOC2R, EOC3L, EOC3R, EOC4L, EOC4R). These individual examination measurements are missing values for between 427 and 454 examinations -- and for 409 examinations, these measurements were missing for all 8 variables. The DCC codebook, however, indicates that there were only 349 missing values for the summary examination score.

COMPARISON TO PUBLISHED ARTICLE.

The published article reviewed evaluates the effect of prior intensive diabetes therapy on neuropathy. The following results, tables, graphs were obtained using a SAS analysis file extracted from the archived export file (*edicNEU8.xpt)* to reproduce the results in the published article. The published results are presented side by side with the values obtained from our dataset integrity check.

RESEARCH DESIGN AND METHODS

The publication reports that there were 1,398 EDIC subjects: 696 subjects from the intensive therapy group and 702 from the conventional therapy group, who had at least one MNSI assessment over the first 8 years of the study.

These numbers were verified. The analysis file contains one record per patient per EDIC year: 1,398 patients, for EDIC years 1-8, 10,543 observations in total.

RESULTS[4]

This paper presents the results of neuropathy status at the end of DCCT, at EDIC onset and up to 8 years into the EDIC study. The analysis investigates the association of neuropathy with original DCCT treatment group and with cumulative and concurrent glycemic levels. The paper also reports lower-extremity events (medical or surgical) associated with neuropathy.

Glycemic control in the EDIC study

Martin et al. begin their presentation by reporting on glycemic control over time in the treatment and control conditions (p. 341). As Table 1 shows, tabulations from the archived data closely match the values published by Martin et al. at DCCT completion, EDIC years 1, 5, and 8.

TABLE 1. Comparison of published HbA_{1c} values and those calculated from archived data by treatment group and time in study.

	PUBLISHED		DATASET CHECK	
TIME	**Intensive**	**Conventional**	**Intensive**	**Conventional**
At DCCT Completion	7.4	9.1	7.3	9.1
EDIC year 1	7.9	8.3	7.9	8.3
EDIC year 5	8.1	8.2	8.1	8.2
EDIC year 8	8.0	7.9	8.0	7.9

Neuropathy status at DCCT completion and EDIC onset

The published article notes that: "At completion of the DCCT, 19.1% of subjects fulfilled the DCCT criteria for definite clinical neuropathy (15.1% of the intensive therapy group and 23.0% of the conventional therapy group (p. 341)." Using the archived outcome variable DCCT_DN and the sample of 1,257 cited in published Table 1, we obtained identical results (19.1% overall, 15.1% for intensive treatment and 23.0% for conditional treatment. Similarly as shown in Table

[4] All our analyses use the MSNI summary scores and binary indicators in the archived dataset --- not variables recalculated from the individual MSNI items.

2, MSNI questionnaire and examination results obtained by tabulating the archived data are identical to those in the published article.

TABLE 2. Subjects satisfying MNSI criteria (questionnaire or examination) for neuropathy at the first annual EDIC study examination by treatment group [n (%)].

	Published		Dataset Check	
MSNI RESULTS	**Conventional**	**Intensive**	**Conventional**	**Intensive**
Ns	633	624	633	624
Positive Questionnaire	30 (4.7)	11 (1.8)	30 (4.7)	11 (1.8)
Positive Examination	177 (28.0)	111 (17.8)	177 (28.0)	111 (17.8)

The published article also reports that prior intense therapy reduced the odds of having symptoms or signs of neuropathy at the beginning of the EDIC. The results summarized in Table 3 indicate that analysis of the archived data yields results that are identical (within rounding error) to the published results.

TABLE 3. Impact of Intensive Therapy on reduction in odds of satisfying MSNI neuropathy criteria (questionnaire or examination) at first EDIC study measurement.

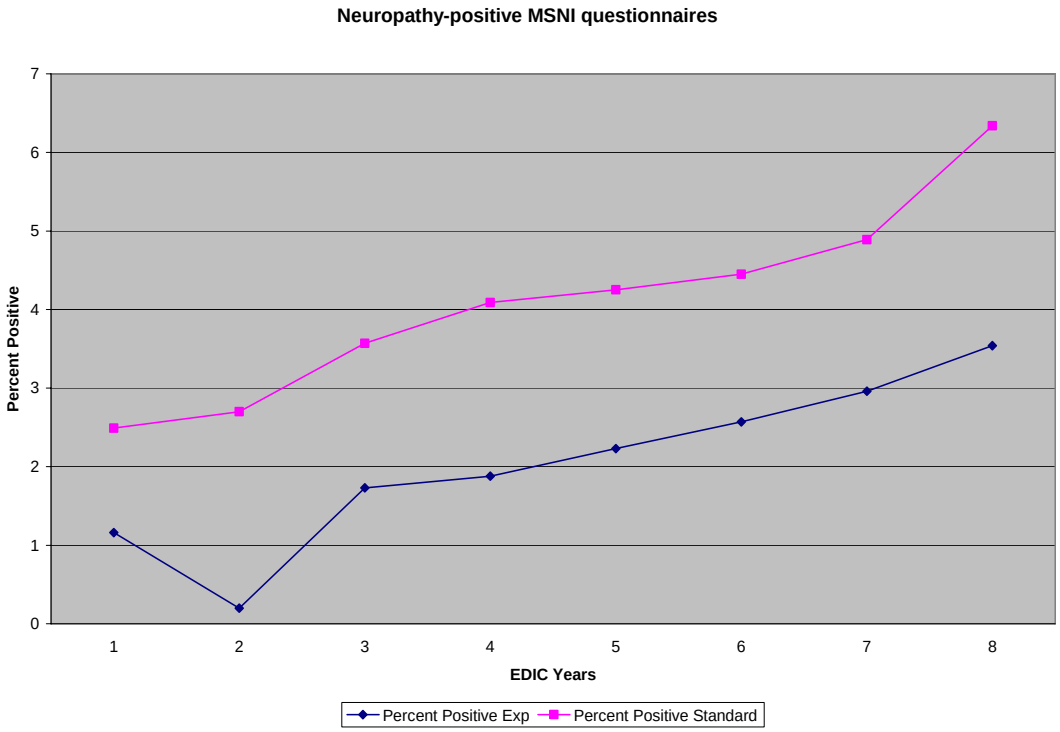
	Reduction in odds of Neuropathy	
MSNI RESULTS	**Published**	**Dataset Check**
Positive on Questionnaire	64% (27%-82%)	64% (27%-82%)
Positive on Examination	45% (27%-58%)	44% (27%-57%)

The published article also compares measures of neuropathy from DCCT and EDIC and reports that "nearly 20% of subjects without neuropathy at DCCT completion fulfilled MNSI examination criteria for neuropathy at first EDIC study evaluation". Our analysis of the archived dataset reproduced this result. Of the 1,238 subjects with no neuropathy at the end of the DCCT, we found that 19.14% fulfilled MSNI examination criteria for neuropathy.

Similarly, the published article reports that "at the first EDIC study evaluation, subjects classified with neuropathy at DCCT completion were 5 times more likely to have a positive MNSI questionnaire (9.7 vs. 1.8%, $p<0.0001$) and nearly twice as likely to have a positive MNSI examination (37.1 vs. 19.7%, $p<0.0001$) as subjects without neuropathy at DCCT completion". Our analysis yielded identical results: 9.7 vs. 1.8% ($p<0.0001$) for a positive MNSI questionnaire result and 37.1 vs. 19.7% ($p<0.0001$) for a positive MNSI examination result.

Persistence of DCCT treatment effect on neuropathy during the EDIC study

The frequency of neuropathy-positive MNSI questionnaires and MNSI examinations across 8 years of the EDIC study were presented in the paper in two figures. We plot below published results and results obtained from our analysis of the same time trends calculated from the archived data. It will be seen that there is high congruence between the published plots and those obtained from analysis of the archived data.



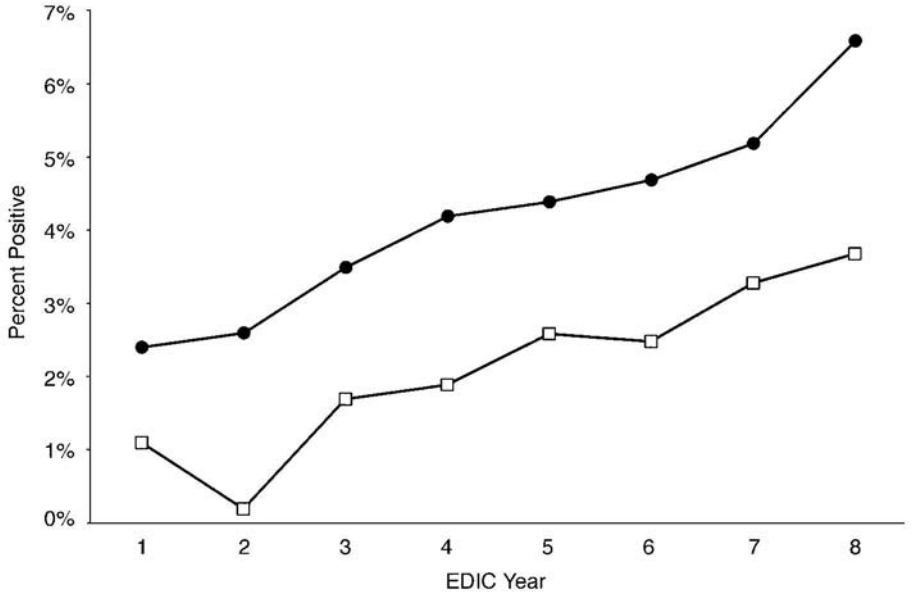
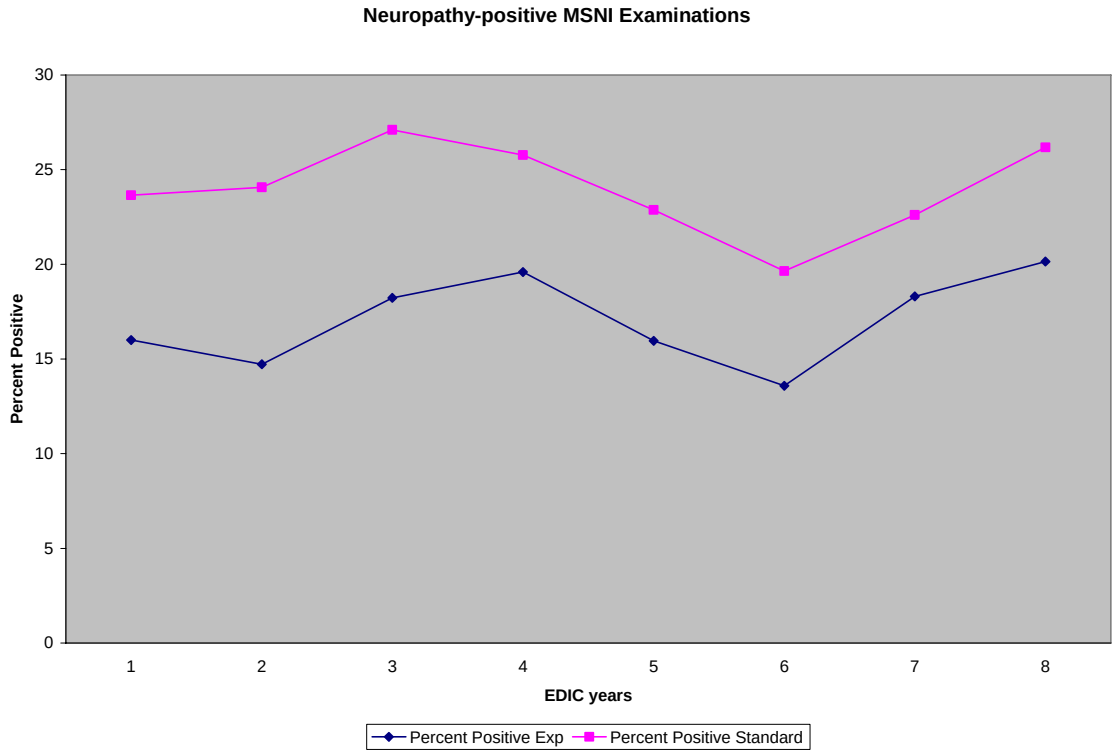


Figure 1—*Frequency of neuropathy-positive MNSI questionnaires across 8 years of the EDIC study among former DCCT conventional therapy (●) and intensive therapy (□) subjects without confirmed clinical neuropathy at the end of the DCCT.* $P < 0.0001$ *on average for all EDIC years combined.*

FIGURE 1. Trends over time by treatment group in the percent of subjects classified as positive on the MSNI neuropathy questionnaire: TOP: Calculated from Archived Data, BOTTOM: published.



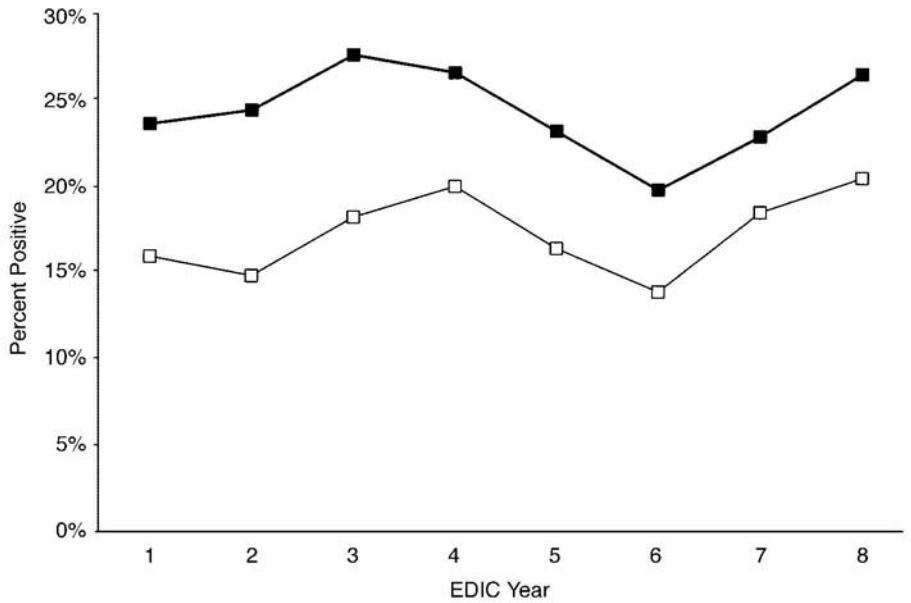


Figure 2—*Frequency of neuropathy-positive MNSI examinations across 8 years of the EDIC study among former DCCT conventional therapy (●) and intensive therapy (□) subjects without confirmed clinical neuropathy at the end of the DCCT.* $P < 0.0001$ *on average for all EDIC years combined.*

FIGURE 2. Trends over time by treatment group in the percent of subjects classified as positive on the MSNI neuropathy examination: TOP: Calculated from Archived Data, BOTTOM: published.

Lower extremities event associated with neuropathy

The paper also reports that during the study, 4 subjects from the intensive therapy group and 11 subjects from the conventional therapy group reported medical or surgical treatment. Also 2 subjects from the former intensive therapy group and five from the conventional therapy group underwent lower extremity amputations. We exactly reproduced the number of these events in our analyses of the archived data.

ATTACHMENT 1

Full Text of Article

Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, Stevens MJ, Feldman EL; DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care.* 2006 Feb;29(2):340-4.

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Neuropathy Among the Diabetes Control and Complications Trial Cohort 8 Years After Trial Completion

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OBJECTIVE — To evaluate the impact of prior intensive diabetes therapy on neuropathy among former Diabetes Control and Complications Trial (DCCT) participants.

RESEARCH DESIGN AND METHODS — At the conclusion of the DCCT, subjects in the intensive group were encouraged to maintain intensive therapy, and subjects in the conventional group were encouraged to begin intensive therapy. Thereafter, we annually assessed neuropathy as part of the Epidemiology of Diabetes Intervention and Complications (EDIC) study. Neuropathy was defined using the Michigan Neuropathy Screening Instrument (MNSI). We recorded potential adverse consequences of neuropathy.

RESULTS — At the first EDIC examination, 1,257 subjects participated in the neuropathy assessment. Consistent with DCCT results, the former intensive group showed a lower prevalence of neuropathy than the conventional group based on positive questionnaire (1.8 vs. 4.7%; $P = 0.003$) or examination (17.8 vs. 28.0%; $P < 0.0001$) results. Despite similar levels of glycemic control, symptoms and signs of neuropathy remained less prevalent among the former intensive group compared with the conventional group. At the beginning of the EDIC study, prior intensive therapy reduced the odds of having symptoms and signs of neuropathy using MNSI criteria by 64% ($P = 0.0044$) and 45% ($P < 0.0001$), respectively, with similar odds reductions observed for both neuropathic symptoms (51%, $P < 0.0001$) and neuropathic signs (43%, $P < 0.0001$) across 8 years of EDIC follow-up.

CONCLUSIONS — The benefits of 6.5 years of intensive therapy on neuropathy status extended for at least 8 years beyond the end of the DCCT, similar to the findings described for diabetic retinopathy and nephropathy.

Diabetes Care 29:340–344, 2006

The Diabetes Control and Complications Trial (DCCT) used a combination of self-reported symptoms, detailed neurological examinations, and nerve conduction studies to identify symptoms, signs, or electrophysiological evidence of distal symmetrical peripheral neuropathy (1,2). The primary neurological end point in the DCCT was the development of "confirmed clinical neuropathy" between baseline and completion of the DCCT, whereas "definite clinical neuropathy" (symptoms and signs consistent with clinical neuropathy as determined by a board-certified neurologist) served as a secondary end point (1–3). Intensive therapy, designed to achieve glycemic levels as close as possible to the nondiabetic range, reduced the risk of developing confirmed clinical neuropathy by 60–69%, with similar reductions noted for definite clinical neuropathy (1–3).

The Epidemiology of Diabetes Intervention and Complications (EDIC) study is an epidemiologic follow-up of the DCCT cohort (4). The primary study goal is to examine the long-term effects of prior intensive compared with conventional therapy on the development and progression of diabetes complications and cardiovascular disease in type 1 diabetes. Surveillance of neuropathy in the EDIC study is performed annually by the EDIC nurse coordinator or diabetologist using the Michigan Neuropathy Screening Instrument (MNSI) (4,5), a 15-item self-administered patient questionnaire adapted from the Neuropathy Symptom Profile of Dyck et al. (6) and a structured foot examination. In the current analyses, we examined whether the difference in neuropathy status observed between intensive and conventional therapy groups during the DCCT persisted after completion of the DCCT, a time when both treatment groups achieved similar levels of glycemic control.

RESEARCH DESIGN AND METHODS

— The DCCT design and eligibility criteria have been described elsewhere (1). Briefly, 1,441 subjects with a 1- to 15-year history of type 1 diabetes who were free of severe neuropathy (defined as neuropathy requiring medical intervention or treatment) and who had no or only minimal, microvascular complications were eligible to participate. Subjects were randomly assigned to intensive therapy (administering insulin three or more times daily by injection or by an external insulin pump) or conventional therapy (one to two injections of insulin daily) (7). Subjects were followed for 4–9 years (mean 6.5) (1). After completion of the DCCT, subjects in the intensive therapy group were encouraged to maintain intensive therapy and subjects in the conventional therapy group were instructed in and encouraged to adopt intensive therapy. All subjects were referred to their personal physicians for their diabetes and

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A list of the people and institutions participating in the DCCT/EDIC Research Group appears in the APPENDIX.
Abbreviations: DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Intervention and Complications; MNSI, Michigan Neuropathy Screening Instrument.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Subjects satisfying MNSI criteria (questionnaire or examination) for neuropathy at the first annual EDIC study examination, separated by DCCT treatment group*

	DCCT treatment group		
	Conventional	Intensive	*P*
n	633	624	
Neuropathy at EDIC study year 1			
Positive questionnaire	30 (4.7)	11 (1.8)	<0.0001
Positive examination	177 (28.0)	111 (17.8)	<0.0001

Data are *n* (%), unless otherwise indicated.

general health care needs. EDIC study annual examinations began in 1994, 1 year after completion of the DCCT. Approximately 95% of the surviving DCCT cohort participated in the follow-up evaluations (4). There were 1,398 EDIC subjects: 696 subjects from the intensive therapy group and 702 from the conventional therapy group, who had at least one MNSI assessment over the first 8 years of the study. EDIC nurse coordinators and diabetologists were trained in a central session and certified to perform the MNSI in the EDIC study. No systematic attempt was made to conceal the prior DCCT group assignment of individual subjects from the nurse coordinator or diabetologist performing the examination.

Outcome measures

Neuropathy status was ascertained annually by EDIC study personnel trained and certified to administer the MNSI, a validated instrument used to identify symptoms and signs of clinically evident neuropathy (4). The MNSI consists of a 15-item questionnaire and a structured examination. Neuropathic symptoms were assessed using the MNSI questionnaire, which inquires about positive (burning, tingling) and negative (numbness) sensory symptoms, cramps and muscle weakness, foots ulcers or cracks, and prior diagnoses of diabetic neuropathy by a physician. Neuropathic signs were assessed using the MNSI examination, a structured assessment of the feet to identify deformities, dry skin, calluses, infection, fissure, or ulcers, and evaluation of ankle reflexes and vibration sensation in the great toe. For this study, neuropathy was defined operationally as seven or more positive responses on the MNSI questionnaire or a score >2.0 on the MNSI examination, thresholds defined by prior validation studies (5,8). The criterion for a positive MNSI examination, the most objective component of the MNSI, was established to achieve high specificity (95%) and sensitivity (80%), with a positive predictive value of 97% and a negative predictive value of 74% (5). These measures permit us to establish the presence or absence of neuropathy. The MNSI has not been validated as a measure of neuropathy severity. Clinically significant lower-extremity events commonly associated with neuropathy were recorded at each annual EDIC examination, including history or presence of lower-extremity ulcers requiring medical or surgical treatment by a health professional and surgical or traumatic amputations (4).

Glycemic control in the EDIC study

Evaluation of glycemic control was based on measurement of HbA_{1c} (A1C) using the same methods previously described for the DCCT (1). At DCCT completion, A1C was 7.4% in the intensive therapy group and 9.1% in the conventional therapy group ($P < 0.01$). At the first EDIC study examination, A1C separation between DCCT intensive and conventional therapy groups narrowed substantially to 7.9 vs. 8.3% ($P < 0.0001$) (1,9). By the 5th year of the EDIC study, the difference in A1C between groups was no longer significant (8.1 vs. 8.2%, $P = 0.10$) (10,11). By EDIC study year 8, the A1C levels were almost identical for the former intensive and conventional therapy groups (8.0 vs. 7.9%, $P = 0.82$) (11).

Statistical analysis

Analyses were performed according to original DCCT treatment group. Subjects were characterized as fulfilling MNSI questionnaire or MNSI examination criteria for neuropathy in each of the first 8 years of the EDIC study. We compared the frequency of definite clinical neuropathy (as determined by a board-certified neurologist) at the conclusion of the DCCT with neuropathy (as determined using the MNSI) at the first EDIC study evaluation. The effect of the prior DCCT treatment (intensive or conventional therapy) on MNSI neuropathy status and the frequency of lower-extremity events in EDIC study years 1–8 were assessed by contingency χ^2 analyses. The impact of glycemic control on neuropathy status was based on the cumulative mean A1C level (averaged from enrollment in the DCCT to the time of the EDIC neuropathy evaluation) and the concurrent A1C level (obtained at the time of the neuropathy assessment). The marginal odds of achieving a neuropathy-positive outcome (MNSI questionnaire or examination) was estimated using the generalized estimating equations method of Liang and Zeger (12), using a logit link and a Binomial distribution.

RESULTS

Neuropathy status at DCCT completion and EDIC onset

At completion of the DCCT, 19.1% of subjects fulfilled the DCCT criteria for definite clinical neuropathy (15.1% of the intensive therapy group and 23.0% of the conventional therapy group). At the beginning of the EDIC study, 3.3% met the MNSI questionnaire criteria for neuropathy (1.8% intensive therapy and 4.7% conventional therapy), and 22.9% of subjects met the MNSI examination criteria for neuropathy (17.8% intensive therapy and 28.0% conventional therapy) (Table 1). Prior intensive therapy reduced the odds of having symptoms of neuropathy (using the MNSI questionnaire) at the beginning of the EDIC study by 64% (95% CI 27–82%, $P = 0.0044$) and signs of neuropathy (using the MNSI examination) at the beginning of the EDIC study by 45% (27–58%, $P < 0.0001$). Nearly 20% of subjects without neuropathy at DCCT completion fulfilled MNSI examination criteria for neuropathy at the first EDIC study evaluation. At the first EDIC study evaluation, subjects classified with neuropathy at DCCT completion were five times more likely to have a positive MNSI questionnaire (9.7 vs. 1.8%, $P < 0.0001$) and nearly twice as likely to have a positive MNSI examination (37.1 vs. 19.7%, $P < 0.0001$) as subjects without neuropathy at DCCT completion.

Persistence of the DCCT treatment effect on neuropathy during the EDIC study

Despite narrowing of differences in glycemic control between DCCT intensive and conventional therapy groups after completion of the DCCT, prior intensive ther-

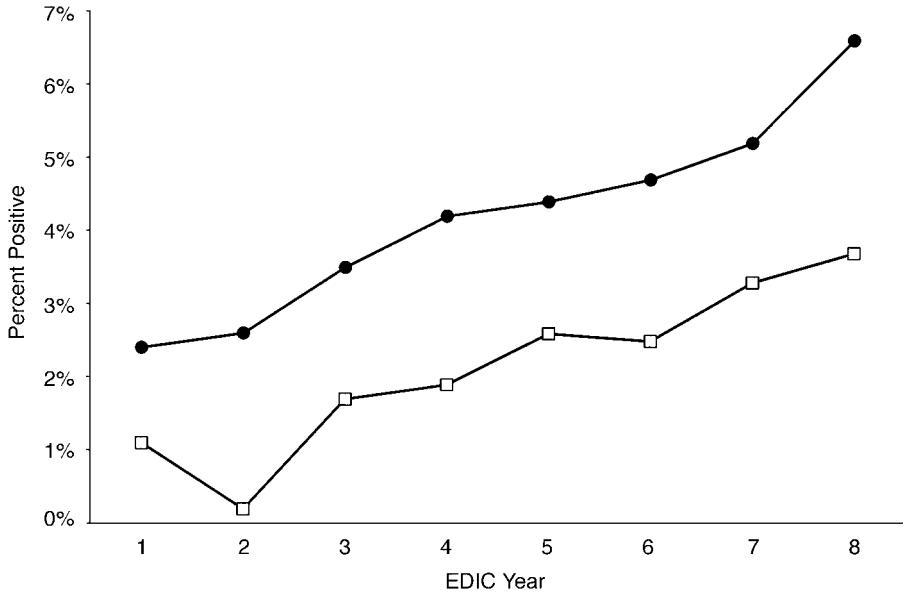

Figure 1—*Frequency of neuropathy-positive MNSI questionnaires across 8 years of the EDIC study among former DCCT conventional therapy (●) and intensive therapy (□) subjects without confirmed clinical neuropathy at the end of the DCCT.* P < *0.0001 on average for all EDIC years combined.*

apy had a durable effect on the MNSI definition of neuropathy based on the questionnaire and the examination among subjects without confirmed clinical neuropathy at the end of the DCCT (Figs. 1 and 2). Across all annual EDIC evaluations, fewer prior intensive therapy subjects had neuropathy by questionnaire ($P < 0.0001$) or by examination ($P < 0.0001$) compared with prior conventional therapy subjects. The likelihood of neuropathy based on the MNSI questionnaire and the MNSI examination was reduced 51% (95% CI 30–66%, $P < 0.0001$) and 43% (33–52%, $P < 0.0001$), respectively, among subjects with prior intensive therapy compared with conventional therapy across 8 years of EDIC follow-up. There was an unexplained decrease in the frequency of a positive MNSI examination observed over EDIC examination years 5 and 6 for both treatment groups relative to the preceding years, but the separation between former conventional and intensive therapy groups remained consistent across all 8 years of EDIC study follow-up.

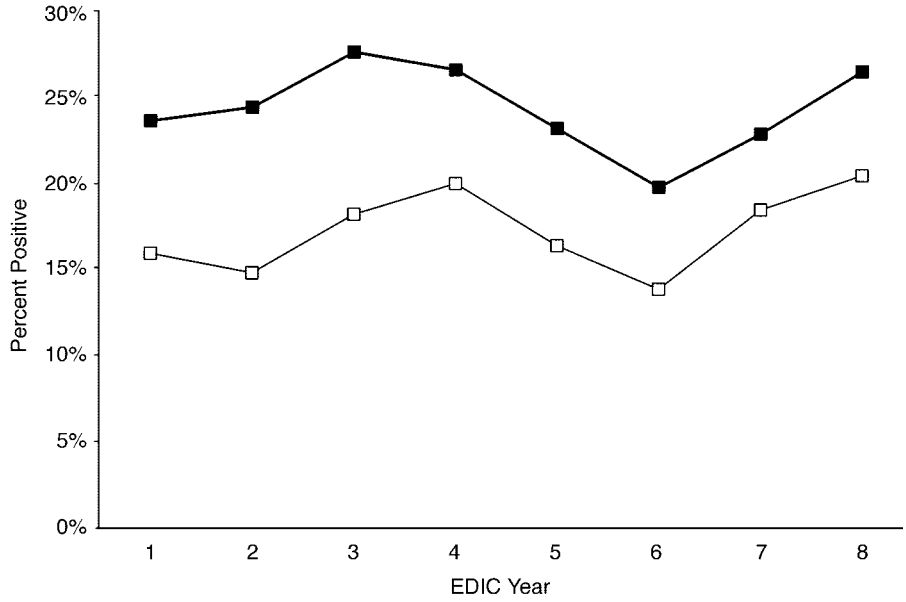

Figure 2—*Frequency of neuropathy-positive MNSI examinations across 8 years of the EDIC study among former DCCT conventional therapy (●) and intensive therapy (□) subjects without confirmed clinical neuropathy at the end of the DCCT.* P < *0.0001 on average for all EDIC years combined.*

Influence of cumulative and concurrent glycemic control on neuropathy

Neuropathy as defined by the MNSI questionnaire and examination was significantly associated with the cumulative mean A1C level. A 1% lower cumulative mean A1C reduced the odds of fulfilling MNSI questionnaire criteria for neuropathy by 38% (95% CI 28–47%, $P < 0.0001$) and MNSI examination criteria for neuropathy by 27% (22–32%, $P < 0.0001$). There was no significant association found between concurrent A1C and either positive MNSI questionnaire or positive MNSI examination.

Lower-extremity events associated with neuropathy

During the study, 15 subjects reported medical or surgical treatment for a total of 22 lower-extremity ulcers (20 foot ulcers and 2 leg ulcers). Fewer subjects in the DCCT intensive therapy group developed foot or leg ulcers than subjects in the conventional therapy group (4 vs. 11, $P = 0.01$). Seven subjects underwent lower-extremity amputations during the first 8 years of the EDIC study. Two were in the former intensive therapy group and five were in the conventional therapy group ($P = 0.45$).

CONCLUSIONS — Neuropathy was defined differently in the DCCT and the EDIC follow-up study. In the DCCT, the diagnosis of definite clinical neuropathy required the presence of symptoms and signs determined by a neurologist to be consistent with a distal symmetrical peripheral neuropathy of the type associated with diabetes. Confirmed clinical neuropathy required additional evidence of nerve conduction abnormalities consistent with diabetic neuropathy. Although it would have been ideal in the EDIC study to repeat the clinical and electrodiagnostic measures, such detailed evaluations were not available in the EDIC study. The EDIC study evaluations used a validated screening instrument to define neuropathy. Despite general agreement

between the results achieved using the two methods, we found a substantially higher prevalence of neuropathy at the start of the EDIC study than at the completion of the DCCT. The prevalence of definite clinical neuropathy we report at the DCCT end differs slightly from that described previously (1,3), which was based on examinations performed after ~5 years in the DCCT, not necessarily at DCCT completion. The neuropathy status at DCCT completion provides the most meaningful comparison to neuropathy status at the beginning of the EDIC study. The higher prevalence of neuropathy found at the beginning of the EDIC study relative to DCCT completion likely reflects the different methodologies and definitions used, rather than interval development of neuropathy. The DCCT definition of neuropathy was more specific than the definition based on the MNSI examination, because it required the clinician to make a clinical judgment based on all available information about competing explanations for any identified signs.

Consistent with the results of the DCCT, we identified significant treatment group differences in the prevalence of neuropathy at the onset of the EDIC study, favoring former intensive therapy over conventional therapy. This group difference in the prevalence of neuropathy persisted over 8 years of EDIC follow-up, despite a narrowing and disappearance of prior glycemic separation. Neuropathy status in the EDIC study was associated with cumulative mean A1C levels from DCCT entry until the EDIC assessment. The finding of a durable effect of prior intensive therapy on the development of neuropathy is consistent with other reports of beneficial effects of metabolic control on neuropathy (13–15) and with the persistent risk reductions with intensive therapy reported for the development and progression of diabetic retinopathy and nephropathy in this cohort (9,11). Although limited by the small number of events, the disproportionate number of subjects developing leg or foot ulcers, favoring former intensive therapy over conventional therapy, is consistent with the conclusion that intensive therapy provided benefits that extended beyond the completion of the DCCT.

In summary, the beneficial effect of intensive therapy on neuropathy status persisted for at least 8 years after completion of the DCCT. The association between antecedent glycemic control and neuropathy status suggests that intensive therapy has a durable effect on clinically evident neuropathy, similar to the previously demonstrated effects on diabetic retinopathy and nephropathy (9,11). Repeat evaluations, including neurological examination and nerve conduction studies identical to those performed in the DCCT, and quantitative sensory testing to better characterize distal sensation are planned in the EDIC study cohort to confirm these preliminary findings and to assess the impact of changes in glycemic control on neuropathy.

Acknowledgments— This work was supported by contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases and the General Clinical Research Centers Program, National Center for Research Resources.

APPENDIX

The DCCT/EDIC Research Group

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APPENDIX B

EDIC 8-Year Neuropathy Analysis Dataset
Check of Summary Statistics

			DCC DOCUMENTATION			CALCULATED FROM ARCHIVED DATASET		
Variable	**Variable Label**	**Category**	**n**	**%**	**Stat.**	**n**	**%**	**Stat.**
Total	Total		10543	.	.	10543	.	.
C_HIGH/ RTI_C_HIGH	MNSI: CLINICAL SCORE > 2	. Missing	349	3.31	.	409	3.88	.
		0: No	7698	73.02	.	7638	72.45	.
		1: Yes	2496	23.67	.	2496	23.67	.
C_SCORE/ RTI_C_SCORE	MNSI: SCORE FROM CLINICAL EXAM	. Missing	349	3.31	.	409	3.88	.
		0	3761	35.67	.	3701	35.10	.
		0.5	275	2.61	.	275	2.61	.
		1	1215	11.52	.	1215	11.52	.
		1.5	225	2.13	.	225	2.13	.
		2	2222	21.08	.	2222	21.08	.
		2.5	315	2.99	.	315	2.99	.
		3	984	9.33	.	984	9.33	.
		3.5	140	1.33	.	140	1.33	.
		4	521	4.94	.	521	4.94	.
		4.5	98	0.93	.	98	0.93	.
		5	312	2.96	.	312	2.96	.
		5.5	41	0.39	.	41	0.39	.
		6	81	0.77	.	81	0.77	.
		7	2	0.02	.	2	0.02	.
		8	2	0.02	.	2	0.02	.
DCCT_DN	DCCT NEUROPATHY	.	167	1.58	.	167	1.58	.
		0: No	8433	79.99	.	8433	79.99	.
		1: Yes	1943	18.43	.	1943	18.43	.
DCCT_HBA	AVERAGE HBA1C DURING DCCT	Mean (N)	10543	.	8.1717	10543	.	8.1717
		STD	.	.	1.4090	.	.	1.4090
		Min	.	.	5.3950	.	.	5.3950
		Max	.	.	13.5750	.	.	13.5750
EDIC_HBA	AVERAGE HBA1C DURING EDIC (THRU CURRENT VISIT)	Mean (N)	10448	.	8.1681	10448	.	8.1681
		STD	.	.	1.2470	.	.	1.2470
		Min	.	.	4.4000	.	.	4.4000
		Max	.	.	15.1000	.	.	15.1000
EDICYEAR	EDIC YEAR	1	1341	12.72	.	1341	12.72	.
		2	1333	12.64	.	1333	12.64	.
		3	1329	12.61	.	1329	12.61	.
		4	1310	12.43	.	1310	12.43	.
		5	1308	12.41	.	1308	12.41	.
		6	1316	12.48	.	1316	12.48	.
		7	1304	12.37	.	1304	12.37	.
		8	1302	12.35	.	1302	12.35	.
EOB1	ARE YOUR LEGS AND/OR FEET NUMB	.	376	3.57	.	376	3.57	.

			DCC DOCUMENTATION			CALCULATED FROM ARCHIVED DATASET		
Variable	Variable Label	Category	n	%	Stat.	n	%	Stat.
		1: No	9351	88.69	.	9351	88.69	.
		2: Yes	816	7.74	.	816	7.74	.
EOB10	FEEL WEAK ALL OVER MOST OF THE TIME	.	372	3.53	.	372	3.53	.
		1: No	9911	94.01	.	9911	94.01	.
		2: Yes	260	2.47	.	260	2.47	.
EOB11	ARE YOUR SYMPTOMS WORSE AT NIGHT	.	415	3.94	.	415	3.94	.
		1: No	9347	88.66	.	9347	88.66	.
		2: Yes	781	7.41	.	781	7.41	.
EOB12	DO YOUR LEGS HURT WHEN YOU WALK	.	377	3.58	.	377	3.58	.
		1: No	9540	90.49	.	9540	90.49	.
		2: Yes	626	5.94	.	626	5.94	.
EOB13	ABLE TO SENSE YOUR FEET WHEN YOU WALK	.	380	3.60	.	380	3.60	.
		1: No	1180	11.19	.	1180	11.19	.
		2: Yes	8983	85.20	.	8983	85.20	.
EOB14	IS SKIN ON FEET SO DRY IT CRACKS OPEN	.	387	3.67	.	387	3.67	.
		1: No	8951	84.90	.	8951	84.90	.
		2: Yes	1205	11.43	.	1205	11.43	.
EOB15	HAVE YOU EVER HAD AN AMPUTATION	.	377	3.58	.	377	3.58	.
		1: No	10113	95.92	.	10113	95.92	.
		2: Yes	53	0.50	.	53	0.50	.
EOB2	EVER HAVE ANY BURNING PAIN IN LEGS/FEET	.	375	3.56	.	375	3.56	.
		1: No	9219	87.44	.	9219	87.44	.
		2: Yes	949	9.00	.	949	9.00	.
EOB3	ARE YOUR FEET TOO SENSITIVE TO TOUCH	.	377	3.58	.	377	3.58	.
		1: No	9817	93.11	.	9817	93.11	.
		2: Yes	349	3.31	.	349	3.31	.
EOB4	GET MUSCLE CRAMPS IN YOUR LEGS/FEET	.	386	3.66	.	386	3.66	.
		1: No	7618	72.26	.	7618	72.26	.
		2: Yes	2539	24.08	.	2539	24.08	.
EOB5	ANY PRICKLING FEELINGS IN LEGS/FEET	.	388	3.68	.	388	3.68	.
		1: No	8548	81.08	.	8548	81.08	.
		2: Yes	1607	15.24	.	1607	15.24	.
EOB6	HURT WHEN BED COVERS TOUCH YOUR SKIN	.	379	3.59	.	379	3.59	.
		1: No	9984	94.70	.	9984	94.70	.
		2: Yes	180	1.71	.	180	1.71	.
EOB7	ARE YOU ABLE TO TELL HOT/COLD WATER	.	373	3.54	.	373	3.54	.
		1: No	681	6.46	.	681	6.46	.
		2: Yes	9489	90.00	.	9489	90.00	.
EOB8	EVER HAD AN OPEN SORE ON YOUR FEET	.	382	3.62	.	382	3.62	.
EOB8	EVER HAD AN OPEN SORE ON YOUR FEET	1: No	8498	80.60	.	8498	80.60	.

			DCC DOCUMENTATION			CALCULATED FROM ARCHIVED DATASET		
Variable	Variable Label	Category	n	%	Stat.	n	%	Stat.
		2: Yes	1663	15.77	.	1663	15.77	.
EOB9	EVER HAD DIABETIC NEUROPATHY	.	402	3.81	.	402	3.81	.
		1: No	8554	81.13	.	8554	81.13	.
		2: Yes	1587	15.05	.	1587	15.05	.
EOCAL	APPEARANCE (L) NORMAL	.	433	4.11	.	433	4.11	.
		1: No	3102	29.42	.	3102	29.42	.
		2: Yes	7008	66.47	.	7008	66.47	.
EOCAR	APPEARANCE (R) NORMAL	.	427	4.05	.	427	4.05	.
		1: No	3104	29.44	.	3104	29.44	.
		2: Yes	7012	66.51	.	7012	66.51	.
EOCB1L	APPEARANCE (L) DEFORMITIES	.	10392	98.57	.	10392	98.57	.
		1: Yes	151	1.43	.	151	1.43	.
EOCB1R	APPEARANCE (R) DEFORMITIES	.	10394	98.59	.	10394	98.59	.
		1: Yes	149	1.41	.	149	1.41	.
EOCB2L	APPEARANCE (L) DRY SKIN, CALLUS	.	8226	78.02	.	8226	78.02	.
		1: Yes	2317	21.98	.	2317	21.98	.
EOCB2R	APPEARANCE (R) DRY SKIN, CALLUS	.	8194	77.72	.	8194	77.72	.
		1: Yes	2349	22.28	.	2349	22.28	.
EOCB3L	APPEARANCE (L) INFECTION	.	10272	97.43	.	10272	97.43	.
		1: Yes	271	2.57	.	271	2.57	.
EOCB3R	APPEARANCE (R) INFECTION	.	10268	97.39	.	10268	97.39	.
		1: Yes	275	2.61	.	275	2.61	.
EOCB4L	APPEARANCE (L) FISSURE	.	10394	98.59	.	10394	98.59	.
		1: Yes	149	1.41	.	149	1.41	.
EOCB4R	APPEARANCE (R) FISSURE	.	10386	98.51	.	10386	98.51	.
		1: Yes	157	1.49	.	157	1.49	.
EOCB5L	APPEARANCE (L) OTHER	.	9871	93.63	.	9871	93.63	.
		1: Yes	672	6.37	.	672	6.37	.
EOCB5R	APPEARANCE (R) OTHER	.	9867	93.59	.	9867	93.59	.
		1: Yes	676	6.41	.	676	6.41	.
EOC2L	ULCERATION (L)	.	453	4.30	.	453	4.30	.
		1: Absent	10029	95.12	.	10029	95.12	.
		2: Present	61	0.58	.	61	0.58	.
EOC2R	ULCERATION (R)	.	427	4.05	.	427	4.05	.
		1: Absent	10050	95.32	.	10050	95.32	.
		2: Present	66	0.63	.	66	0.63	.
EOC3L	ANKLE REFLEXES (L)	.	454	4.31	.	454	4.31	.
		1: Present	6325	59.99	.	6325	59.99	.
		2: Present/Reinforcement	1361	12.91	.	1361	12.91	.
		3: Absent	2403	22.79	.	2403	22.79	.
EOC3R	ANKLE REFLEXES (R)	.	452	4.29	.	452	4.29	.
		1: Present	6350	60.23	.	6350	60.23	.
		2: Present/Reinforcement	1395	13.23	.	1395	13.23	.

			DCC DOCUMENTATION			CALCULATED FROM ARCHIVED DATASET		
Variable	Variable Label	Category	n	%	Stat.	n	%	Stat.
		3: Absent	2346	22.25	.	2346	22.25	.
EOC4L	VIBRATION PERCEPTION AT GREAT TOE (L)	.	448	4.25	.	448	4.25	.
		1: Present	7649	72.55	.	7649	72.55	.
		2: Reduced	2185	20.72	.	2185	20.72	.
		3: Absent	261	2.48	.	261	2.48	.
EOC4R	VIBRATION PERCEPTION AT GREAT TOE (R)	.	445	4.22	.	445	4.22	.
		1: Present	7591	72.00	.	7591	72.00	.
		2: Reduced	2261	21.45	.	2261	21.45	.
		3: Absent	246	2.33	.	246	2.33	.
EOC5L	10 GRAM FILAMENT (L)	.	442	4.19	.	442	4.19	.
		1: Present	9457	89.70	.	9457	89.70	.
		2: Reduced	502	4.76	.	502	4.76	.
		3: Absent	142	1.35	.	142	1.35	.
EOC5R	10 GRAM FILAMENT (R)	.	443	4.20	.	443	4.20	.
		1: Present	9429	89.43	.	9429	89.43	.
		2: Reduced	537	5.09	.	537	5.09	.
		3: Absent	134	1.27	.	134	1.27	.
FSASDATE	DEIDENTIFIED FORMDATE	Mean (N)	10194	.	4115.762	10194	.	4115.762
		STD	.	.	1033.067	.	.	1033.067
		Min	.	.	1788.000	.	.	1788.000
		Max	.	.	6779.000	.	.	6779.000
HBA_DATE	DEIDENTIFIED HBA1C COLLECTION DATE	Mean (N)	10442	.	4098.925	10442	.	4098.925
		STD	.	.	1205.690	.	.	1205.690
		Min	.	.	-24818.0	.	.	-24818.0
		Max	.	.	13212.00	.	.	13212.00
HBAEL	HBA1C BASELINE ELIGIBILITY	Mean (N)	10543	.	9.0402	10543	.	9.0402
		STD	.	.	1.6039	.	.	1.6039
		Min	.	.	6.5600	.	.	6.5600
		Max	.	.	15.4200	.	.	15.4200
HBA1C	CURRENT HBA1C	Mean (N)	10448	.	8.1318	10448	.	8.1318
		STD	.	.	1.3768	.	.	1.3768
		Min	.	.	4.1000	.	.	4.1000
		Max	.	.	16.0000	.	.	16.0000
*PT_HIGH/ RTI_PT_HIGH	MNSI: PATIENT SCORE > 6	.	349	3.31	.	368	3.49	.
		0: No	9650	91.53	.	9631	91.35	.
		1: Yes	544	5.16	.	544	5.16	.
**PT_SCORE/ RTI_PT_SCORE	MNSI: SCORE FROM PATIENT CHECKLIST	.				368		
		0				147		
		1	560	5.31	.	560	5.31	.
		2	4473	42.43	.	4473	42.43	.
		3	2228	21.13	.	2229	21.13	.
		4	1225	11.62	.	1225	11.62	.
		5	600	5.69	.	600	5.69	.

			DCC DOCUMENTATION			CALCULATED FROM ARCHIVED DATASET		
Variable	Variable Label	Category	n	%	Stat.	n	%	Stat.
		6	398	3.78	.	397	3.78	.
		7	206	1.95	.	206	1.95	.
		8	124	1.18	.	124	1.18	.
		9	91	0.86	.	91	0.86	.
		10	55	0.52	.	55	0.52	.
		11	31	0.29	.	31	0.29	.
		12	19	0.18	.	19	0.18	.
		13	13	0.12	.	13	0.12	.
		14	4	0.04	.	4	0.04	.
		15	1	0.01	.	1	0.01	.
SUMAMP	AMPUTATION (EDIC TOTAL)	.: Missing	10488	99.48	.	10488	99.48	.
		1	55	0.52	.	55	0.52	.
SUMFOOT	FOOT ULCERS REQ MED/SURGICAL TREATMENT (EDIC TOTAL)	.: Missing	10440	99.02	.	10440	99.02	.
		1	86	0.82	.	86	0.82	.
		2	8	0.08	.	8	0.08	.
		3	9	0.09	.	9	0.09	.
SUMLEG	LEG ULCERS REQ MED/SURGICAL TREATMENT (EDIC TOTAL)	.: Missing	10528	99.86	.	10528	99.86	.
		1	15	0.14	.	15	0.14	.

APPENDIX C

SAS Programs Used in Dataset Check

TABLES

```
OPTIONS NOFMTERR;
libname data "c:\projects\NIDDK\EDIC\NewData\data";

data neuro_8yr;
   set data.neuro_8yr;


****APPENDIX 3: SUMMARY STATISTICS OF ALL VARIABLES;

   ****  EOB1--EOB15 1 IS NEGATIVE- 2 IS POSITIVE
   ****  NEOB1--NEOB15   0 IS NEGATIVE AND 1 IS POSITIVE;

DO I=1 TO 15;


ARRAY MSNI1 (15)  EOB1 EOB2 EOB3 EOB4 EOB5 EOB6 EOB7 EOB8 EOB9 EOB10 EOB11
                  EOB12 EOB13 EOB14 EOB15;

       MSNI1(I) = MSNI1(I)-1;
    END;


****RECREATING PT_SCORE;
RTI_PT_SCORE = SUM(EOB1,EOB2,EOB3,EOB4,EOB5,EOB6,EOB7,EOB8,
                  EOB9,EOB10,EOB11,EOB12,EOB13,EOB14,EOB15);

****REPRODUCING PT_HIGH FROM PT_SCORE;
IF RTI_PT_SCORE > 6 THEN RTI_PT_HIGH=1;
   ELSE IF 0<=RTI_PT_SCORE<=6 THEN RTI_PT_HIGH=0;
   ELSE RTI_PT_HIGH=.;

****RECREATING C_SCORE;
IF SUM(EOCAL,EOCAR,EOC2L,EOC2R,EOC3L,EOC3R,EOC4L,EOC4R)=. THEN RTI_C_SCORE=.;
   ELSE RTI_C_SCORE= ROUND(SUM(
(EOCAL = 1),
(EOCAR = 1),
(EOC2L = 2),
(EOC2R = 2),
(0.5 * (EOC3L = 2) + (EOC3L = 3)),
(0.5 * (EOC3R = 2) + (EOC3R = 3)),
(0.5 * (EOC4L = 2) + (EOC4L = 3)),
(0.5 * (EOC4R = 2) + (EOC4R = 3))));

****REPRODUCING C_HIGH FROM C_SCORE;
IF RTI_C_SCORE >2 then RTI_C_HIGH=1;
   ELSE IF RTI_C_SCORE = . THEN RTI_C_HIGH=.;
   ELSE IF RTI_C_SCORE <=2 THEN RTI_C_HIGH=0;


LABEL
  DCCT_DN  ='DCCT NEUROPATHY'
  DCCT_HBA ='AVERAGE HBA1C DURING DCCT'
  EDIC_HBA ='AVERAGE HBA1C DURING EDIC'
  HBAEL='HBA1C BASELINE ELIGIBILITY'
  HBA1C='CURRENT HBA1C';

****N=10543;

TITLE 'APPENDIX 3: SUMMARY STATISTICS OF ALL VARIABLES';


PROC FREQ; TABLES  C_SCORE RTI_C_SCORE C_HIGH RTI_C_HIGH/MISSING;

PROC FREQ; TABLES DCCT_DN EDICYEAR/MISSING;
```

```
PROC MEANS; VAR DCCT_HBA EDIC_HBA;

PROC FREQ;
   TABLES NEOB1 NEOB2 NEOB3 NEOB4 NEOB5 NEOB6 NEOB7 NEOB8
          NEOB9 NEOB10 NEOB11 NEOB12 NEOB13 NEOB14 NEOB15/MISSING;

PROC FREQ;
   TABLES EOCAL EOCAR EOCBIL EOCBIR EOCB2L EOCB2R EOCB3L EOCB3R EOCB4L EOCB4R
          EOCB5L EOCB5R EOC2L EOC2R EOC3L EOC3R EOC4L EOC4R EOC5L EOC5R/MISSING;

PROC MEANS;
   VAR FSASDATE HBA_DATE HBAEL HBA1C;

PROC FREQ; TABLES PT_HIGH RTI_PT_HIGH PT_SCORE RTI_PT_SCORE /MISSING;

PROC FREQ; TABLES SUMAMP SUMFOOT SUMLEG/MISSING;

RUN;
*****************************************************************************;

********************REPRODUCE TABLES AND NUMBERS FROM MANUSCRIPT*****************;

**1- RESEARCH DESIGN AND METHODS*************************************************
* THERE WERE 1,398 EDIC SUBJECTS: 696 EXPERIMENTAL (INTENSIVE TX) AND 702
* STANDARD TX WITH AT LEAST ONE ASSESSMENT IN 8 YRS
*************************************************************************;


PROC SORT DATA=NEURO_8YR;
   BY MASK_PAT;

****AT LEAST ONE ASSESSMENT IN 8 YEARS;
DATA NEURO;
   SET NEURO_8YR;
   BY MASK_PAT;
   IF LAST.MASK_PAT;
RUN;

PROC FREQ; TABLES GROUP;
RUN;

*****************************************************************************
**2- OUTCOME MEASURES (page 341);
*****************************************************************************

PROC FREQ DATA=NEURO_8YR;
   TABLES PT_HIGH*RTI_PT_HIGH/MISSING;

PROC FREQ DATA=NEURO_8YR;
   TABLES C_HIGH*RTI_C_HIGH/MISSING;



**3- GLYCEMIC CONTROL IN THE EDIC STUDY (page 341)******************;
**TRYING TO REPRODUCE VALUES AT DCCT COMPLETION (7.4% AND 9.1% P<0.01)************
**RTI gets 7.3 and 9.1
*******************************************************************************;


DATA YEAR1;
   SET NEURO_8YR;
   IF EDICYEAR=1;
RUN;

OPTIONS LS=132 PAGENO=1;;
PROC SORT DATA=YEAR1; BY GROUP;
PROC TTEST DATA=YEAR1; VAR DCCT_HBA ; CLASS GROUP;
RUN;
```

```
**REPRODUCING VALUES AT 1, 5 AND 8 YEARS OF EDIC*******;

PROC SORT DATA=NEURO_8YR;
   BY GROUP;
PROC TTEST; VAR HBA1C; CLASS GROUP; WHERE EDICYEAR=1 ;
TITLE 'AIC AT EDIC - YEAR 1';

PROC SORT DATA=NEURO_8YR;
   BY GROUP;
PROC TTEST; VAR HBA1C; CLASS GROUP; WHERE EDICYEAR=5 ;
TITLE 'AIC AT EDIC - YEAR 5';

PROC SORT DATA=NEURO_8YR;
   BY GROUP;
PROC TTEST; VAR HBA1C; CLASS GROUP; WHERE EDICYEAR=8 ;
TITLE 'AIC AT EDIC - YEAR 8';
RUN;





***4- RESULTS************************************;

***1- NEUROPATHY STATUS AT DCCT COMPLETION AND EDIC ONSET;
***N=1257 (633 and 624);

DATA YEAR1A;
   SET NEURO_8YR;
   IF EDICYEAR=1;
   IF GROUP='EXPERIMENTAL' THEN NGROUP=1;
     ELSE IF GROUP='STANDARD' THEN NGROUP=0;
IF PT_SCORE NE . OR C_SCORE NE .; *n=1257;

PROC FREQ DATA=YEAR1A;
   TABLES DCCT_DN*NGROUP;
   TITLE 'NEUROPATHY STATUS AT COMPLETION OF DCCT';
RUN;


*******************************************************************************
* BEGINNING OF EDIC STUDY 3.3% + ACCORDING TO MSNI QUESTIONNAIRE FOR NEUROPATHY
* (1.8 AND 4.7)                                                               *
* AND 22.9 + ACCORDING TO MSNI EXAMINATION (17.8% AND 28.0%)                  *
* THIS IS TABLE 1                                                             *
*******************************************************************************;

PROC FREQ DATA=YEAR1A;
   TABLES PT_HIGH*NGROUP;
   TITLE 'EDIC STUDY YEAR 1: NEUROPATHY ACCORDING TO MNSI QUESTIONNAIRE';
RUN;

PROC FREQ DATA=YEAR1A;
   TABLES C_HIGH*NGROUP;
   TITLE 'EDIC STUDY YEAR 1: NEUROPATHY ACCORDING TO MNSI EXAMINATION';

RUN;



*******************************************************************************
* PRIOR INTENSIVE THERAPY REDUCED ODDS OF HAVING SYMTOMS (MSNI QUESTIONNAIRE)    *
* AT BEGINNING OF EDIC BY 64% (95% CI 27-82%, P=0.0044) AND SIGNS OF NEUROPATHY  *
* BY 45% (27%-58%, P<0.0001.                                                     *
* ****************************************************************************;

PROC FREQ; TABLES NGROUP*PT_HIGH/CMH;
TITLE 'ODDS OF HAVING SYMPTOMS';
```

```
run;

PROC FREQ; TABLES NGROUP*C_HIGH/CMH;
TITLE 'ODDS OF HAVING SIGNS';
run;


*******************************************************************************
* MNSI questionnaire criteria for neuropathy                                  *
* Case-Control      Mantel-Haenszel        0.3607       0.1791       0.7263    *
*                                                                             *
* OR 0.36  (0.18-0.73) for intensive therapy compared with standard           *
* ---> 64% decrease (27%-82%) - ok!!!  p=0.003 (not 0.0044)                   *
*                                                                             *
* MNSI symtoms for neuropathy                                                 *
* Case-Control      Mantel-Haenszel        0.5574       0.4261       0.7293    *
* ---> 45% decrease (27%-58%) - ok!!!  p < 0.0001                             *
*******************************************************************************




*******************************************************************************
* 20% of subjects w/o neuropathy at DCCT show neuropathy at first EDIC exam   *
* OK!!                                                                        *
*******************************************************************************;

DATA YEAR1A;
   SET NEURO_8YR;
   IF EDICYEAR=1;
   IF GROUP='EXPERIMENTAL' THEN NGROUP=1;
     ELSE IF GROUP='STANDARD' THEN NGROUP=0;
IF PT_SCORE NE . OR C_SCORE NE .; *n=1257;
PROC FREQ; TABLES DCCT_DN*C_HIGH;
TITLE 'TABLE WITH EDIC VARIABLES';
run;

*******************************************************************************
*MANUSCRIPT:
* SUBJECTS DCCT_DN=1  5 TIMES MORE LIKELY TO HAVE + QUESTIONNAIRE (9.7 VS 1.8%  *
*                     P <0.0001                                               *
*                                                                             *
*                     2 TIMES MORE LIKELY TO HAVE + EXAMINATION (37.1 VS 19.7%  *
*                     P <0.0001                                               *
*******************************************************************************;

PROC FREQ DATA=YEAR1A; TABLES DCCT_DN*PT_HIGH/CMH;
TITLE 'TABLE WITH EDIC VARIABLES';
run;

PROC FREQ DATA=YEAR1A; TABLES DCCT_DN*C_HIGH/CMH;
TITLE 'TABLE WITH EDIC VARIABLES';
run;

*******************************************************************************
*results   :                                                                  *
* subjects dcct_dn=1  questionnaire or=5.87 (9.7 vs 1.8%)  p <.0001           *
*                                                                             *
*                                                                             *
*                     examination or=2.4  (37.1 vs 19.7%)  p <.0001           *
*                                                                             *
*******************************************************************************;


*******************************************************************************
* PERSISTENCE OF THE DCCT TREATMENT EFFECT ON NEUROPATHY OVER 8 YEARS EDIC STUDY *
*******************************************************************************;
```

```
****VALUES FOR GRAPHIC;

DATA NEUROPATHY;
   SET NEURO_8YR;
   IF DCCT_DN=0;
PROC SORT; BY EDICYEAR;
PROC FREQ; TABLES GROUP*PT_HIGH; BY EDICYEAR;
RUN;

PROC FREQ; TABLES GROUP*C_HIGH; BY EDICYEAR;
RUN;

*******************************************************************************
* values for graphic- do not see dip in neuropathy-positive msni questionnaire    *
* for experimental treatment at 6 yrs-                                            *
*                                                                                 *
* questionaire:                                                                   *
*                                                                                 *
* experimental    1.16      0.2     1.73    1.88    2.23    2.57    2.96    3.54  *
* standard        2.49      2.70    3.57    4.09    4.25    4.45    4.89    6.34  *
*                                                                                 *
* examination:                                                                    *
*                                                                                 *
* experimental    16.0      14.72   18.23   19.59   15.96   13.58   18.30   20.15 *
* standard        23.65     24.07   27.10   25.77   22.87   19.64   22.61   26.18 *
*******************************************************************************;



*********************************************
**MANUSCRIPT- LOWER EXTREMITY EVENTS ASSOCIATED WITH
NEUROPATHY*************************************
* 15 SUBJECTS REPORTED TOTAL 22 LOWER EXTREMITIES ULCERS (20 FOOT AND 2 LEG ULCERS

* FEWER SUBJECTS IN THE DCCT INTENSIVE THERAPY GROUP DEVELOPED FOOT OR LEG ULCERS THAN
SUBJECTS
* IN CONVENTIONAL THERAPY GROUP 4 VS 11 P=0.01.
*
* 7 SUBJECTS UNDERWEN LOWER EXTREMITIES AMPUTATIONS 2 FROM THE FORMER THERAPY
INTENSIVE GROUP
* AND 5 IN THE CONVENTIONAL THERAPY GROUP 2 VS 5 P=0.45



data ulcers;
   set neuro_8yr;
   if sumfoot ne . or sumleg ne .;
proc sort;
   by mask_pat;

data ulcers1;
   set ulcers;
   by mask_pat;
   if first.mask_pat;
proc freq; tables sumfoot sumleg;
run;
proc print; var mask_pat sumfoot sumleg;
run;

*******************************************************************************
****NOTE:
*****# of lower extremity events- numbers match the 15 22 and (22 2) from the manuscript
*******************************************************************************;

data abn;
   set neuro_8yr;
proc sort data=abn;
   by mask_pat;
```

```
data abn1;
   set abn;
   by mask_pat;
   if first.mask_pat;
   if sumfoot ne . or sumleg ne . then ulcers=1;
      else ulcers=0;
   if sumamp = . then sumamp=0;
proc freq;
   tables group*ulcers/chisq;
   title 'lower extremity eventsby DCCT tx';
run;

***#s are 4 vs 11 but p=0.072 and not 0.01;

proc freq data=abn1;
   tables group*sumamp/chisq;
   title 'amputations';
run;


*****************************************
******RESULTS:
****#s are 2 vs 5 but p=0.26 and not 0.;
*****************************************:

PROC PRINT;  WHERE C_SCORE=0 AND RTI_C_SCORE=.;
  VAR EOCAL EOCAR EOC2L EOC2R EOC3L EOC3R EOC4L EOC4R;
  title 'check the raw values for discordant results';

GENMOD ANALYSIS

***OVERALL DIFFERENCES OVER 8 YEARS OF EDIC;


*****all these were attempts to try to reproduce the sections in the manuscript
"Persistence of the DCCT treatment effect on neuropathy during the EDIC study"
and
"Influence of cumulative and concurrent glycemic control on neuropathy"
;

*****Only the figures were included in the report-
*****************************************************************************
* MANUSCRIPT: MSNI QUESTIONNAIRE REDUCED 51% 95CI 30%-66%  P<0.0001              *
*             MSNI EXAMINATION REDUCED 43% 95CI 33%-52%    P<0.0001              *
*****************************************************************************;

OPTIONS LS=132 PAGENO=1;

PROC GENMOD DATA=NEUROPATHY DESCENDING;
   CLASS MASK_PAT GROUP;
   MODEL PT_HIGH = GROUP  /DIST=BIN LINK=LOGIT;
   REPEATED SUBJECT=MASK_PAT/TYPE=EXCH /*COVB CORRW*/;
   TITLE 'OVERALL DIFFERENCES IN MSNI QUESTIONNAIRE OVER 8 YEARS OF EDIC';
RUN;

PROC GENMOD DATA=NEUROPATHY DESCENDING;
   CLASS MASK_PAT GROUP;
   MODEL C_HIGH = GROUP/DIST=BIN LINK=LOGIT;
   REPEATED SUBJECT=MASK_PAT/TYPE=EXCH  COVB CORRW;
   TITLE 'OVERALL DIFFERENCES IN MSNI EXAMINATION OVER 8 YEARS OF EDIC';
RUN;


data OR_QUEST;

beta=-0.7309;
beta1=-1.207;
beta2=-0.2546;
```

```
OR=EXP(beta);
OR95LL=EXP(BETA1);
OR95HL=EXP(beta2);

proc print; var OR OR95LL OR95HL;
   TITLE 'OR AND 95% CI FOR DIFFERENCES IN MSNI QUESTIONNAIRE OVER 8 YEARS EDIC';
run;



data OR_EXAM;

beta=-0.445;
beta1=-0.635;
beta2=-0.25;

OR=EXP(beta);
OR95LL=EXP(BETA1);
OR95HL=EXP(beta2);

proc print; var OR OR95LL OR95HL;
   TITLE 'OR AND 95% CI FOR DIFFERENCES IN MSNI EXAMINATION OVER 8 YEARS EDIC';
run;
```

the likelihood of neuropathy based on the MSNI questionnaire and the MSNI examination was reduced 51% (95% CI 30-66%, p<0.0001) and 43% (33-52%, p<0.0001) respectively, among subjects with prior intensive therapy compared with conventional therapy across 8 years of EDIC follow-up

```
*******************************************************************************
* results:                                                                    *
*                                                                             *
* questionnaire-                                                              *
*                                    standard   95% confidence                *
* parameter              estimate    error       limits         z pr > |z|    *
*                                                                             *
* intercept               -3.1191   0.1528  -3.4185  -2.8196  -20.41   <.0001 *
* group     experimental  -0.7301   0.2430  -1.2064  -0.2537   -3.00   0.0027 *
* group     standard       0.0000   0.0000   0.0000   0.0000     .      .     *
*
* or = 0.48186  95% ci 0.29927    0.77592
*                                                                             *
* examination-                                                                *
*                                                                             *
*                                    standard   95% confidence                *
* parameter              estimate    error       limits            z pr > |z| *
*                                                                             *
* intercept               -1.1538   0.0657  -1.2825  -1.0251  -17.57   <.0001 *
* group     experimental  -0.4406   0.0968  -0.6304  -0.2509   -4.55   <.0001 *
* group     standard       0.0000   0.0000   0.0000   0.0000                  *
*
* or = 0.64365  95% ci 0.53238    0.77810
*******************************************************************************;

*******************************************************************************
* MANUSCRIPT: MSNI QUESTIONNAIRE REDUCED 51% 95CI 30%-66%  P<0.0001           *
*             MSNI EXAMINATION REDUCED 43% 95CI 33%-52%    P<0.0001           *
*******************************************************************************;

****************?????????DIFFERENCES?????????????????????????????????????????;
```

MANUSCRIPT- INFLUENCE OF CUMULATIVE AND CONCURRENT GLYCEMIC CONTROL ON NEUROPATHY**************

```
* NEUROPATHY (QUESTIONNAIRE AND EXAMINATION) ASSOCIATED WITH CUMULATIVE MEAN A1C LEVEL
*
* A 1% LOWER CUMULATIVE MEAN A1C REDUCED THE ODDS OF FULFILLING MNSI QUESTIONNAIRE
CRITERIA       *
* FOR NEUROPATHY BY 38% (95% CI 38-47%, P<0.0001) AND MNSI EXAMINATION CRITERIA
*
* FOR NEUROPATHY BY 27% (95% CI 22-32%, P<0.0001)
*
* NO SIGNIFICANT ASSOCIATION FOUND BETWEEN CONCURRENT A1C AND EITHER POSITIVE MNSI
QUESTIONNAIRE  *
* OR EXAMINATION
*
*******************************************************************************
************;

OPTIONS NOCENTER PAGENO=1 LS=132;
TITLE1 'INFLUENCE OF CUMULATIVE AND CONCURRENT GLYCEMIC CONTROL ON NEUROPATHY';

PROC GENMOD DATA=NEURO_8YR DESCENDING;
   CLASS MASK_PAT GROUP;
   MODEL PT_HIGH = GROUP HBA1C EDIC_HBA/DIST=BIN LINK=LOGIT;
   REPEATED SUBJECT=MASK_PAT/TYPE=EXCH /*COVB CORRW*/;
   TITLE2 'MODEL INCLUDES: TREATMENT, CUMULATIVE AND CONCURRENT GLYCEMIC CONTROL';
RUN;
PROC GENMOD DATA=NEURO_8YR DESCENDING;
   CLASS MASK_PAT GROUP;
   MODEL PT_HIGH = GROUP HBA1C /DIST=BIN LINK=LOGIT;
   REPEATED SUBJECT=MASK_PAT/TYPE=EXCH /*COVB CORRW*/;
   TITLE2 'MODEL INCLUDES: TREATMENT AND CONCURRENT GLYCEMIC CONTROL';
RUN;
PROC GENMOD DATA=NEURO_8YR DESCENDING;
   CLASS MASK_PAT GROUP;
   MODEL PT_HIGH = GROUP EDIC_HBA/DIST=BIN LINK=LOGIT;
   REPEATED SUBJECT=MASK_PAT/TYPE=EXCH /*COVB CORRW*/;
   TITLE2 'MODEL INCLUDES: TREATMENT AND CUMULATIVE GLYCEMIC CONTROL';
RUN;
PROC GENMOD DATA=NEURO_8YR DESCENDING;
   CLASS MASK_PAT GROUP;
   MODEL PT_HIGH = HBA1C EDIC_HBA/DIST=BIN LINK=LOGIT;
   REPEATED SUBJECT=MASK_PAT/TYPE=EXCH /*COVB CORRW*/;
   TITLE2 'MODEL INCLUDES: CUMULATIVE AND CONCURRENT GLYCEMIC CONTROL';
RUN;
PROC GENMOD DATA=NEURO_8YR DESCENDING;
   CLASS MASK_PAT GROUP;
   MODEL PT_HIGH = EDIC_HBA/DIST=BIN LINK=LOGIT;
   REPEATED SUBJECT=MASK_PAT/TYPE=EXCH /*COVB CORRW*/;
   TITLE2 'MODEL INCLUDES:  CUMULATIVE GLYCEMIC CONTROL';
RUN;
PROC GENMOD DATA=NEURO_8YR DESCENDING;
   CLASS MASK_PAT GROUP;
   MODEL PT_HIGH = HBA1C DIST=BIN LINK=LOGIT;
REPEATED SUBJECT=MASK_PAT/TYPE=EXCH /*COVB CORRW*/;
   TITLE2 'MODEL INCLUDES: CONCURRENT GLYCEMIC CONTROL';
RUN;


***NOTE: manuscript says no significant association found between concurrent a1c and
either positive mnsi questionnaire*
*        or examination. i found association- doing year by year- alone in model or
after adjusting by prior treatment *
*        also overall - with treatment and without there is significant association
*
*        manuscript results: a 1% lower cumulative mean a1c reduced the odds
*
                             for positive questionnaire by 38% (95% ci 28-47%,
p<0.0001)                                  *
                             for positive examination by 27% (95% ci 22-32%, p<0.0001)
*
```

```
* equivalent to get odds ratio of 0.62 (95% 0.53-0.72) and 0.73 (0.68-0.78)  can't
reproduce                              *
************************************************************************
*
```