SUPPLEMENTAL MATERIALS

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Table S1. MNSI-survey: 15-item self-report questionnaire

		Yes	No
Instructions: Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check yes or no based on how you usually feel. Thank you.			
•	Are your legs and/or feet numb?	1	0
•	Do you ever have any burning pain in your legs and/or feet?	1	0
•	Are your legs and/or feet too sensitive to touch?	1	0
•	Do you get muscle cramps in your legs and/or feet?	0	0
•	Do you ever have any prickling feelings in your legs and/or feet?	1	0
•	Does it hurt when the bed covers touch your skin?	1	0
•	When you get into the tub or shower, are you able to tell the hot water from the cold water?	0	1
•	Have you ever had an open sore on your foot?	1	0
•	Has your doctor ever told you that you have diabetic neuropathy?	1	0
•	Do you feel weak all over most of the time?	0	0
•	Are your symptoms worse at night?	1	0
•	Do your legs hurt when you walk?	1	0
•	Are you able to sense your feet when you walk?	0	1
•	Is the skin on your feet so dry that it cracks open?	1	0
•	Have you ever had an amputation?	1	0

Scoring: Responses to the MNSI-survey are added to obtain a total score. Responses of "yes" to items 1-3, 5-6, 8-9, 11-12, 14-15 are each counted as one point each, and "no" responses to items 7 and 13 count as 1 point each. The MNSI-survey was considered normal if the score was <4.

Table S2. MNSI-exam: 4-item examination

Neuropathy Screening Instrument						
	LEFT FOOT			**RIGHT FOOT**		
• Appearance and condition of both feet	0 Normal	1 Abnormal		0 Normal	1 Abnormal	
	If ABNORMAL, *(check all that apply)*			*If ABNORMAL,* *(check all that apply)*		
• Deformities	☐ 1			☐ 1		
• Dry skin, callus	☐ 1			☐ 1		
• Infection	☐ 1			☐ 1		
• Fissure	☐ 1			☐ 1		
• Other (specify: _____)	☐ 1			☐ 1		
• Ulceration	1 Present	0 Absent		1 Present	0 Absent	
• Ankle reflexes	0 Present	0.5 Present/ Reinforcement	1 Absent	0 Present	0.5 Present/ Reinforcement	1 Absent
• Vibration perception at great toe	0 Present (< 10 sec)	0.5 Reduced (10 sec)	1 Absent	0 Present (< 10 sec)	0.5 Reduced (10 sec)	1 Absent
• 10gm filament (record number of applications detected)	0 Present (8)	1 Reduced (1–7)	1 Absent (0)	0 Present (8)	1 Reduced (1–7)	1 Absent (0)

Scoring: 1) Each foot with any abnormality received a score of 1; 2) each foot with an ulcer receives a score of 1; 3) vibration sensation was considered normal (0 points) if at the time the participant stopped feeling the vibration the examiner would continue to feel it on the dorsum of their thumb for less than an additional 10 seconds; it was scored as impaired (0.5 points) if the examiner felt it for >10 seconds and absent (1 point) if the participant could not feel the vibration at all; and 4) reflexes at the ankle were considered normal (0 points); reduced (0.5 points) if they could only be elicited with the Jendrassic maneuver; and absent (1 point) if they could not be

elicited even with the Jendrassic maneuver. The total possible score was added across both feet to get a possible 0 to 8 points. The MNSI-exam was considered normal if the score (across both feet) was ≤ 2.

Table S3. Baseline demographic and metabolic characteristics of TODAY participants (n=674) by abnormal MNSI-exam or monofilament during the study[*]
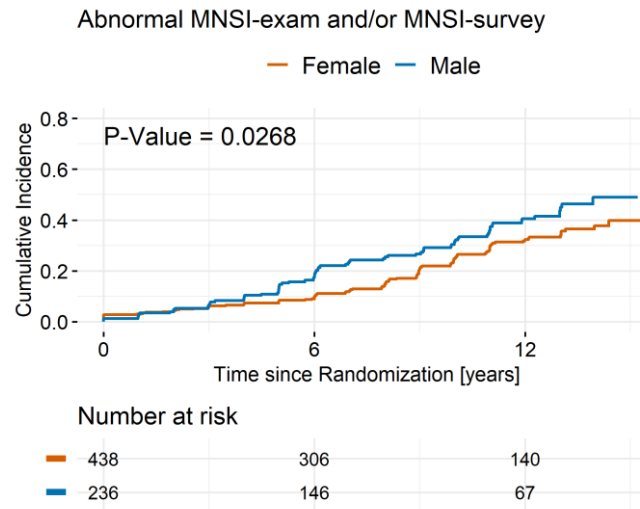
	Normal MNSI-exam (n=528)	Abnormal MNSI-exam (n=146)	P-value	Normal Monofilament (n=643)	Abnormal Monofilament (n=31)	P-value
Male (%)	32.4%	44.5%	0.007	34.1%	54.8%	0.02
Race-ethnicity (%)						
Black non-Hispanic	32.8%	34.9%	ns	32.7%	45.2%	ns
Hispanic	39.4%	41.8%		40.1%	35.5%	
White non-Hispanic	19.9%	17.2%		19.6%	12.9%	
Other	7.9%	6.2%		7.6%	6.4%	
Age (years)	13.9 ± 2.0	14.3 ± 1.9	0.03	14.0 ± 2.0	14.2 ± 2.1	ns
Diabetes duration (months)	7.9 ± 6.0	7.3 ± 5.3	ns	7.8 ± 5.8	7.7 ± 5.3	ns
Maternal diabetes (%)	44.3%	48.2%	ns	44.8%	53.3%	ns
Smoking in past month (%)	4.4%	2.1%	ns	3.9%	3.2%	ns
HbA1c (%)	6.0 ± 0.7	6.1 ± 0.8	ns	6.0 ± 0.7	6.2 ± 0.7	ns
BMI (kg/m^2)	34.3 ± 7.1	38.0 ± 8.8	<.0001	35.0 ± 7.5	36.8 ± 9.9	ns
BMI Z-score	2.2 ± 0.5	2.4 ± 0.5	<.0001	2.2 ± 0.5	2.4 ± 0.5	ns
Blood pressure (mm Hg)						
Systolic	113.0 ± 10.5	114.8 ± 12.2	ns	113.3 ± 10.8	114.2 ± 12.4	ns
Diastolic	66.8 ± 8.1	67.0 ± 8.7	ns	66.9 ± 8.3	65.0 ± 6.1	ns
LDL cholesterol (mg/dL)	85.4 ± 25.2	84.4 ± 22.2	ns	85.2 ± 24.7	84.3 ± 21.7	ns
HDL cholesterol (mg/dL)	38.4 ± 8.4	39.5 ± 9.3	ns	38.7 ± 8.7	38.1 ± 6.4	ns
Total cholesterol (mg/dL)	146.6 ± 30.0	145.2 ± 26.4	ns	146.4 ± 29.2	143.4 ± 29.5	ns
Triglycerides (mg/dL)	96 [66 -137]	89 [67 - 131]	ns	95 [67 - 136]	87 [66 – 150]	ns
Urine ACR (mg/g)	7 [5 - 14]	7 [5 - 13]	ns	7 [5 - 14]	7 [4 – 22]	ns
Vitamin B12 level category (%)						
Low (≤ 203 pg/mL)	3.5%	2.8%	ns	3.5%	0.0%	ns
Borderline low (204 - ≤ 298 pg/mL)	21.8%	21.8%		21.7%	22.6%	
Normal (> 298 pg/mL)	74.8%	75.3%		74.8%	77.4%	

Table S4. Most frequent abnormal responses on the MNSI-survey and MNSI-exam at baseline (randomization), year 7 and year 14

MNSI-survey	Baseline (n=670)	Year 7 (n=446)	Year 14 (n=175)
Muscle cramps in legs and/or feet	37.0%	22.6%	36.0%
Prickling feelings in legs and/ or feet	19.4%	13.7%	26.9%
Not able to sense foot when walking	16.1%	7.6%	9.1%
Ever had an open sore on foot	15.5%	10.1%	14.3%
Can't tell hot from cold water	11.3%	6.5%	13.1%
Skin on feet so dry that it cracks open	10.1%	10.1%	10.3%
Legs hurt when walking	6.1%	4.5%	8.6%
Burning pain in legs and/or feet	5.2%	4.9%	14.9%
Feel weak all over most of the time	4.5%	3.8%	12.6%
Legs and/or feet feel too sensitive to touch	3.0%	2.7%	12.0%
Legs and/or feet feel numb	2.5%	4.3%	10.9%
Symptoms worse at night	2.2%	1.8%	13.1%
Doctor told you have diabetic neuropathy	1.3%	2.0%	10.9%
Pain when bed cover touches skin	0.5%	0.7%	3.4%
Ever had an amputation	0.2%	0.4%	1.7%
MNSI-exam	**Baseline (n=674)**	**Year 7 (n=458)**	**Year 14 (n=175)**
Reduction/absence of ankle reflex	11.1%	22.5%	44.0%
Dry skin, callus	10.5%	28.2%	26.9%
Reduction/absence of vibration at great toe	3.0%	11.6%	29.1%
Infection	2.1%	2.0%	4.6%
Ulcer	1.6%	0.7%	4.6%
Fissure	1.5%	2.8%	1.1%
Deformities	0.7%	2.2%	3.4%

Figure S1. Cumulative incidence of combined abnormal MNSI-exam (score >2) and/or MNSI-survey (score ≥4) by sex during TODAY [*]

Abnormal MNSI-exam and/or MNSI-survey

— Female — Male

P-Value = 0.0268

Cumulative Incidence

Time since Randomization [years]

Number at risk

	0	6	12
Female	438	306	140
Male	236	146	67

[*] Kaplan-Meier cumulative incidence probability curves for the DPN outcomes, with number of participants at risk at 0, 6, and 12 years. The number at risk beyond year 12 declines as a function of staggered entry into the cohort from 2004 to 2008. P-value for difference by sex based on log-rank test.

Table S5. Associations between retinopathy, vascular stiffness, and heart rate variability with presence of abnormal MNSI-exam or monofilament during the study

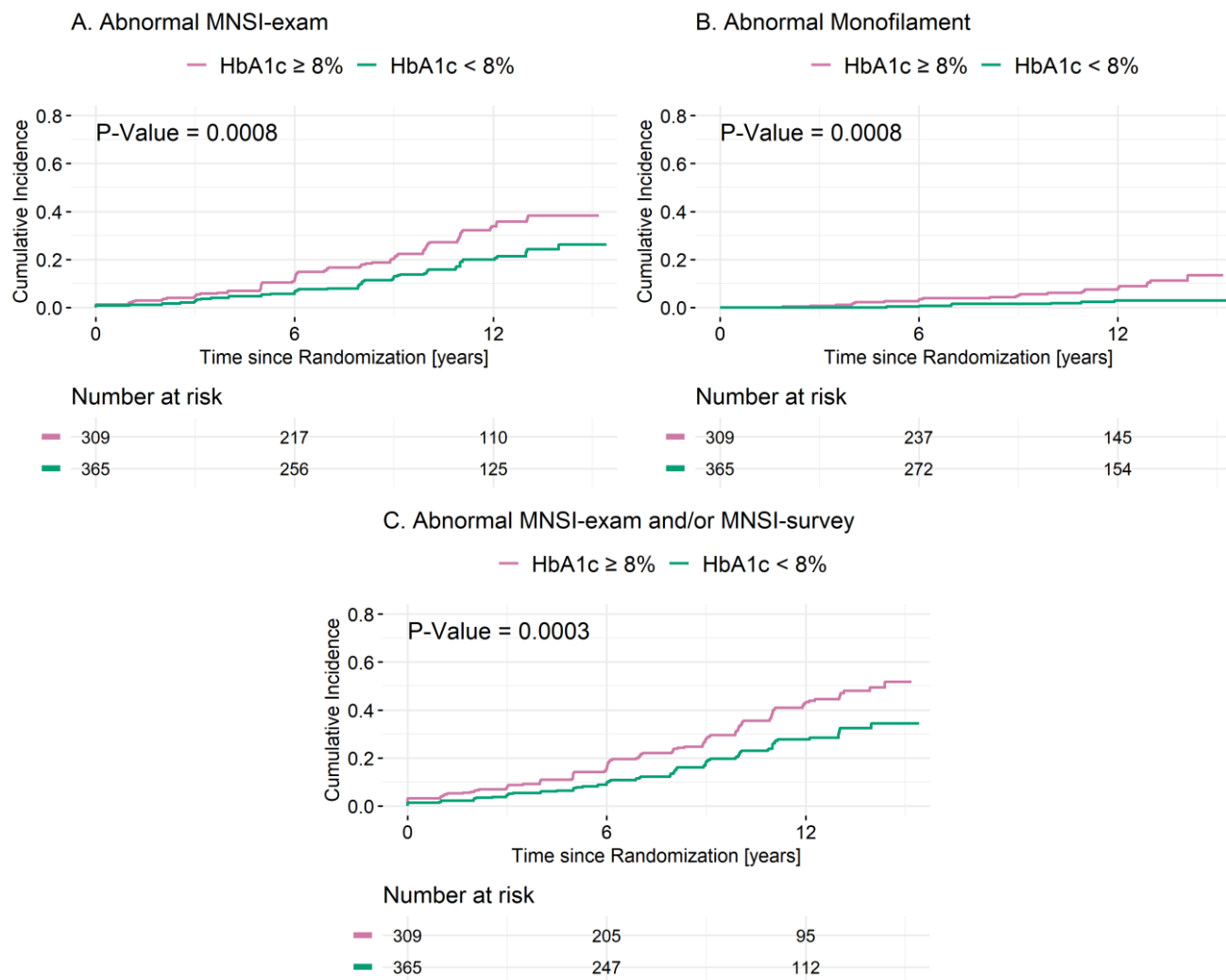|	Normal MNSI-exam	Abnormal MNSI-exam	P-value	Normal Monofilament	Abnormal Monofilament	P-value
Diabetic Retinopathy[*]						
N of participants with data available	272	115		365	22	
Retinopathy at the 7-year follow-up assessment (%)	46.7%	50.4%	0.50	46.6%	68.2%	0.06
Retinopathy progression (%)	24.4%	30.3%	0.24	24.8%	47.6%	0.03
Vascular stiffness[†]						
N of participants with data available	217	103		299	21	
Carotid-femoral PWV at the 5-year follow-up assessment (m/s)	7.1 ± 1.8	7.3 ± 1.6	0.03	7.1 ± 1.7	7.6 ± 1.9	0.009
Heart rate variability[‡]						
N of participants with data available	257	124		357	22	
SDNN at the 5-year follow-up assessment (ms)	49.6 ± 29.2	42.7 ± 28.5	0.005	48.0 ± 29.3	37.2 ± 24.3	0.03

Data are N or percent of participants, or mean $\pm$ SD. Retinopathy, vascular stiffness, and heart rate variability data were not available for all participants. P-values obtained from unadjusted chi-square tests for categorical variables and t-tests for continuous variables.

[*] Retinopathy was assessed 7 years apart via fundus photography, and defined as Early Treatment Diabetic Retinopathy Study (ETDRS) grade $\geq$ 20 in either eye or presence of clinically significant macular edema. A $\geq$3-step progression on the ETDRS scale was defined as retinopathy progression.

[†] Vascular stiffness was assessed 5 years apart using the SphygmoCor device. PWV: pulse wave velocity. Higher values of carotid-femoral PWV indicate worsening.

[‡] Heart rate variability was assessed 5 years apart and determined from an electrocardiogram. SDNN: standard deviation of the NN intervals. Lower values of SDNN indicate worsening.

Figure S2. Cumulative incidence of abnormal MNSI-exam (A), monofilament (B) and combined abnormal MNSI-exam and/or MNSI-survey (C) by loss of glycemic control, defined as reaching primary outcome during TODAY (sustained HbA1c ≥8%)[*]

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