Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Methods S1. Neuropsychological battery and dementia detection protocol

The dementia psychometric battery includes clock drawing[1], verbal fluency[2], Mattis Dementia Rating Scale[3], Boston naming[2], verbal paired associations and recall, logical memory and recall[4], Word List Memory[2], Constructional Praxis and recall[2], Trails A and B[5], and Information and Comprehension subtest items[4]. All clinical data are reviewed at a consensus conference. If dementia is diagnosed, clinical laboratories and imaging results are considered in assigning dementia subtype (e.g. Alzheimer's disease, thyroid disease, normal pressure hydrocephalus, vascular dementia, etc.). When these results are not available from medical records, they are requested to be ordered by the delivery system, results are obtained, and then reviewed again at a subsequent consensus conference.

Dementia onset is assigned half way between the prior biennial and the exam that diagnosed dementia. These procedures have been used since 1986. ACT incidence rates are consistent with those found worldwide[6], supporting the validity of our case definitions. Furthermore, forest plots of associations between alleles of single nucleotide polymorphisms and dementia from Alzheimer's disease suggest similar strength of association for cases and controls ascertained by the ACT study as those from more than a dozen other research studies of dementia from Alzheimer's disease[7].

The ACT neuropsychological battery is characterized by good assessment of executive functioning (Mattis initiation and concept scales, comprehension, Trails, fluency, and clock drawing) which would aid in identification of vascular cognitive impairment / vascular dementia and fronto-temporal dementia. There is good assessment of spatial ability (clock and Mattis construction) that would help with the diagnosis of Lewy body dementia and Parkinson's disease with dementia. It should be emphasized that the diagnostic process is based not only on psychometric test results but especially historical and clinical elements considered by an expert consensus of clinicians and neuropsychologists using all available data including results from the psychometric tests.

Methods S2. Glucose level exposure.

The objective of this analysis was to develop a measure of average daily glucose levels in the prior *M* years based on clinical laboratory measures of glucose, total glycated hemoglobin, and hemoglobin A1c (HbA1c). We selected an analytic strategy that allowed us to combine information on glucose levels from these measures, while stabilizing estimates for individuals with relatively sparse observations by borrowing information across participants and accounting for the relative variability of glucose and HbA1c measures in creating our combined estimate. This approach was motivated by the joint survival and continuous exposure modeling methods of Dafni and Tsiatis[8].

Our analytic approach used a hierarchical Bayesian framework to construct a daily average glucose level in the prior *M* years based on a weighted average of glucose and HbA1c measures transformed to the glucose scale using the equation of Nathan et al.[9] Let X_{ij} represent the *j*th glucose measures for the *i*th participant and Y_{ij} represent the *j*th measure of glucose in the time period of interest estimated from HbA1c for participant *i*. We assume the hierarchical model

$$\begin{aligned} X_{ij} &\sim N(\mu_i, \sigma_X^2), \\ Y_{ij} &\sim N(\mu_i, \sigma_Y^2), \\ \mu_i &\sim N(\theta, \tau^2), \end{aligned}$$

where μ_i represents the average daily glucose level for the *i*th individual in the time period of interest. This model assumes that, given a participant's average daily glucose level, measured glucose and glucose estimated from HbA1c or total glycated hemoglobin are independent and vary randomly around an individual's daily average with variance σ_X^2 and σ_Y^2, respectively, and that in the population of interest average daily glucose levels vary across individuals with population mean θ and variance τ^2. Let n_{iX} represent the total number of glucose measures available in the prior *M* years for subject *i* and n_{iY} denote the total number of total glycated hemoglobin or HbA1c measures available. We adopt an empirical Bayes estimation framework, thus prior distributions for θ and τ^2 were not required. Under this approach, the posterior distribution for μ_i is normal with mean

$$\widetilde{\mu}_i = E(\mu_i \mid \overline{X}_i, \overline{Y}_i, \sigma_X^2, \sigma_y^2, \theta, \tau^2) = A\overline{X}_i + B\overline{Y}_i + C\theta,$$

and variance

$$V = Var(\mu_i \mid X_i, Y_i, \sigma_X^2, \sigma_y^2, \theta, \tau^2) = \frac{\sigma_X^2 \sigma_Y^2 \tau^2}{\sigma_X^2 \tau^2 n_{iY} + \sigma_Y^2 \tau^2 n_{iX} + \sigma_X^2 \sigma_Y^2},$$

where $\overline{X}_i$ is the mean of the glucose measures in the prior *M* years for individual *i*, $\overline{Y}_i$ is the mean of glucose estimated based on HbA1c measures in the prior *M* years for individual *i*, $A = \dfrac{V}{\sigma_X^2 / n_{iX}}$,

$B = \dfrac{V}{\sigma_Y^2 / n_{iY}}$, and $C = \dfrac{V}{\tau^2}$.

We used $\tilde{\mu}_i$ as our estimate of average daily glucose level. This estimate is a weighted average of the sample means for glucose and glucose estimated based on total glycated hemoglobin or HbA1c and the prior or population mean, θ. The posterior mean will be more heavily weighted towards a participant's average glucose or HbA1c estimated glucose the larger the sample size of these measures. Similarly, the more variable these measures are about the true daily average glucose level, the smaller the weight they will receive in the average. For participants with few observations available, their average will be heavily shrunk towards the population mean.

To obtain estimates of θ and τ^2 we adopted an empirical Bayes approach[10]. This approach uses the prior predictive distribution of $\overline{X}$ and $\overline{Y}$ to estimate prior parameters. Estimates based on the mean and variance of the prior predictive distribution are given by

$$\hat{\theta} = \frac{\sum_{i=1}^{N}\left(\overline{X}_i + \overline{Y}_i\right)}{\sum_{i=1}^{N}(1(n_{iX} > 0) + 1(n_{iY} > 0))},$$

$$\hat{\tau}^2 = \max(0, s_{XY} - \frac{\sum_{i=1}^{N}\left(\sigma_X^2 / n_{iX} + \sigma_Y^2 / n_{iY}\right)}{\left(\sum_{i=1}^{N}(1(n_{iX} > 0) + 1(n_{iY} > 0))\right)^2}),$$

where 1(.) is the indicator function which takes the value of one if the condition in parentheses is satisfied and zero otherwise, *N* is the total number of subjects in the study population, and $s_{XY} = \frac{\sum_{i=1}^{N}((\overline{X}_i + \overline{Y}_i)/(1(n_{iX} > 0) + 1(n_{iY} > 0)) - \hat{\theta})^2}{N}$. These estimates are then substituted into the expressions for the posterior mean and variance.

Finally, estimates for σ_X^2 and σ_Y^2 were based on prior information about variability in glucose measures and glucose estimated using total glycated hemoglobin or HbA1c. The variance of glucose around its daily average, i.e. σ_X^2, was estimated using data from Nathan et al.[9] Their study data consisted of glucose levels (mg/dL) measured on people with and without diabetes every 5 minutes over the course of 2-3 days at multiple study visits spread out over 12 weeks. See Nathan et al. for a more thorough discussion of their study data[9]. Using a subset of their glucose data (limited to participants aged 50-69 with either Type 2 diabetes or no diabetes), we first computed an estimate of an average daily glucose for each subject-day (based on the subject's 5 minute glucose measures from that day). We then computed the differences between this average daily glucose and each of these 5 minute measures for each subject-day, and computed the variance of these differences across all subject-days, separately for those with and without diabetes. This yielded $\sigma_X^2 = 18.3^2$ for those without diabetes and $\sigma_X^2 = 42.5^2$ for those with diabetes. Variance of glucose around its daily average using glucose estimated from HbA1c measures, i.e. σ_Y^2, was based on the standard errors for predicted glucose using the

predictive equation of Nathan et al.[9] This was taken to be $\sigma_Y^2 = 15.7^2$ and was the same for those with and without diabetes.

Estimates of $\widetilde{\mu}_i$ were obtained separately for subjects with and without diabetes. We thus assumed that the distribution of average daily glucose levels was normally distributed about a population mean for subjects without diabetes and around a separate mean for those with diabetes.

Methods S3. Relationship between primary glucose level exposure and a simpler glucose level exposure

The glucose level exposure measure described in Supplemental Methods S2 is somewhat complicated. We chose this more complicated approach for three primary reasons: to incorporate all of the available glucose level data, to enable us to account for the different variability in hemoglobin A1c values relative to glucose values, and to help stabilize glucose level estimates for individuals with sparse measures.

It may be of interest to consider a simpler glucose level exposure measure. As such, here we show a much simplified approach to determining glucose level exposure over a five year period, and the association between this simpler exposure measure and the one we used in our primary analyses.

For the simpler glucose level exposure estimate, we consider the available laboratory values for each participant.

a. If they have only glucose values in the five year period – with no hemoglobin A1c or total glycated hemoglobin measures, their exposure is calculated as the mean of their glucose values.
b. If they have only hemoglobin A1c values, only total glycated hemoglobin values, or a combination of glycated hemoglobin and hemoglobin A1c values, then any total glycated hemoglobin values are transformed to hemoglobin A1c values using the formula in the manuscript, and then the Nathan et al. formula[9] is used to calculate the A1c-derived average daily glucose associated with each hemoglobin A1c value. The glucose level exposure is calculated as the mean of the A1c-derived average daily glucose values.
c. If they have a combination of glucose values and either total glycated hemoglobin or hemoglobin A1c values, then omit the glucose values, and consider only the more informative total glycated hemoglobin and hemoglobin A1c values, as in b above. The rationale for this approach is that derived average daily glucose values receive much more weight in the exposure used in the paper, and random glucose values do not have much of an effect on overall exposure in the face of any hemoglobin A1c or total glycated hemoglobin values.

We performed these calculations for the cohort included in the analyses at study baseline, and compared these simpler estimated exposure values to those included in our primary analyses. For people without diabetes, the correlation between the two values was 0.92, while for people with diabetes, the correlation was 0.98. Ignoring random glucose values has a greater effect on people who had a large number of glucose values available.

Scatter plots of the average glucose levels over the five years preceding baseline using the simpler strategy (on the x axis) and using the strategy employed in the paper (y axis) are shown in Figure S6.

Methods S4. Further details of potential confounders.

Physical activity was defined based on responses to ACT questionnaires at each study visit that asked "How many days per week did you do each of the following for at least 15 minutes at a time (0=none, 7=daily). A. Walking for exercise; B. Hiking; C. Bicycling or exercycle; D. Aerobics and calisthenics; E. Swimming; F. Water aerobics; G. Weight training or strengthening; H. Other exercise (specify)." Days were summed across these items and then this total was dichotomized at up to 2 vs. 3 or more, as we did in an earlier publication focused on physical activity[11].

Coronary artery disease was defined based on endorsement of ACT questionnaires at each study visit that included a question about whether a doctor ever (study entry) or since the previous visit (subsequent visits) told the participant that they had any of the following: G2: Heart attack / coronary; G3: Angina pectoris; G7: Coronary bypass surgery; and G8: Balloon angioplasty. Affirmative responses to any of these four items was coded as presence of coronary artery disease; negative responses to all of these four items was coded as absence of coronary artery disease.

Cerebrovascular disease was similarly defined based on endorsement of ACT questionnaires. The same stem question was followed with G5: Stroke, cerebral hemorrhage, or apoplexy; G6: Small strokes / TIAs; and G9: Surgery on arteries of neck. As for coronary artery disease, affirmative responses to any of these items was coded as presence of cerebrovascular disease; negative responses to all of these three items was coded as absence of cerebrovascular disease.

Atrial fibrillation was based on one or more ICD-9 codes 427.3, 427.31, or 427.32 from any encounter type.

Methods S5. Sensitivity of Bayesian approach to assumptions for prior distributions.

Because the weighting of the components of $\tilde{\mu}_i$ depends on the relative magnitude of σ_X^2, σ_Y^2, and τ^2, we also conducted four sensitivity analyses varying the magnitudes and ratios of these values:

Sensitivity 1 (Model B): Increase magnitude of variability but maintain relative magnitude of variability for glucose and HbA1c:

$\sigma_X^2 = (2*18.3)^2$ with diabetes; $\sigma_X^2 = (2*42.5)^2$ without diabetes; $\sigma_Y^2 = (2*15.7)^2$

Sensitivity 2 (Model C): Decrease magnitude of variability but maintain relative magnitude of variability for glucose and HbA1c:

$\sigma_X^2 = (0.5*18.3)^2$ with diabetes; $\sigma_X^2 = (0.5*42.5)^2$ without diabetes; $\sigma_Y^2 = (0.5*15.7)^2$

Sensitivity 3 (Model D): Increase magnitude of variability for measures based on glucose

$\sigma_X^2 = (2*18.3)^2$ with diabetes; $\sigma_X^2 = (2*42.5)^2$ without diabetes; $\sigma_Y^2 = 15.7^2$

Sensitivity 4 (Model E): Decrease magnitude of variability for measures based on HbA1c

$\sigma_X^2 = 18.3^2$ with diabetes; $\sigma_X^2 = 42.5^2$ without diabetes; $\sigma_Y^2 = (0.5*15.7)^2$

Methods S6. Accounting for prandial status of glucose laboratory values.

Prandial status is unknown for most of the glucose values from the clinical laboratory data base. A small proportion of laboratory values carried the label of "fasting glucose". We were concerned that treating these values the same as those for which prandial status was unknown might introduce bias to our estimates.

To address this concern, we turned again to the Nathan et al. data [9]. We identified the lowest single glucose value for each participant in each day to approximate the fasting value, and determined the difference between that value and the average daily glucose for that person. We then determined the average across all people who did not have diabetes, and the average across all people who had Type 2 diabetes. We then applied this correction factor to all glucose values from the clinical laboratory data that carried the "fasting glucose" label. We re-ran all analyses with these augmented values.

While the single lowest glucose level in a day is certainly a fasting value, it is likely that samples obtained in actual clinical practice do not capture that precise moment in the day; most of the samples producing values labeled as "fasting glucose" would have a value somewhat closer to the average daily glucose than the single lowest value of the day. The sensitivity analyses with the correction for prandial status based on average differences between the single lowest glucose value and the average daily glucose thus represent an upper bound for how much difference accounting for prandial status could have on our results; the truth likely lies somewhere in between the unadjusted analyses presented in the paper and those using this likely extreme correction factor.

Methods S7. Authorship roles.

The ACT study was designed by Eric Larson with Walter Kukull and Gerald van Belle.

The present analyses were designed by an analysis group that included Paul Crane, Rod Walker, Rebecca Hubbard, Gail Li, and Sebastien Haneuse. The group of Steven Kahn, Suzanne Craft, and Tom Montine provided guidance to the analysis group on diabetes and modeling glucose levels.

Data were gathered over many years by the ACT staff, supervised by Dr. Larson in his role as study PI. Data for detection of dementia are obtained by trained psychometrists and experienced physicians (Drs. Larson, James Bowen, and Wayne McCormick) and a study nurse (Meredith Pfanschmidt, RN). These individuals review data in a consensus conference along with a study neuropsychologist (Dr. Linda Teri for several years, and more recently Dr. Susan McCurry). Clinical data were gathered using Group Health laboratory facilities. Data to populate the glucose level model were contributed by Drs. David Nathan and Hui Zheng from the A1c-Derived Average Glucose (ADAG) study.

Mr. Walker was the primary data analyst, supervised by Drs. Hubbard and Crane. All three of them vouch for the analyses.

Dr. Crane wrote the first draft of the paper. All authors supplied critical intellectual content to the first draft, which Dr. Crane incorporated in subsequent drafts of the paper. All authors approved the final manuscript. The decision to publish the paper was mutual by all authors.

The National Institutes of Health (the sponsor of the ACT study) had no influence on the decision to publish the paper and no requirements to keep any aspect of the data confidential.

Methods S8. Details of spline models.

Rather than assume a strict linear relationship between glucose levels and risk of dementia, which is what would be specified if a simple continuous linear term for glucose levels were included in the regression model, we chose instead to allow for a more flexible non-linear association. We achieved this flexibility by modeling the relationship between glucose levels and dementia risk using splines.

Splines are piecewise polynomials used in curve fitting that can be used to approximate potentially complex functional forms. The polynomials are piecewise in that they are specified over intervals of the domain of *X* (e.g., the exposure), with the endpoints of these intervals referred to as the knots of the spline. The first and last knots placed within the domain are called the boundary knots, while the others are referred to as interior knots. Splines can vary in regard to the degree and form of the piecewise polynomials used, the number and spacing of the knots along the domain, and the restrictions on how the polynomials behave at the knots. Many splines impose constraints that higher order polynomials join 'smoothly' at the knots, thus allowing for better ability to approximate highly curved relationships.

In this glucose analysis we used natural cubic splines. This is a type of spline specification that utilizes cubic polynomials but forces smooth joins at interior knots (by requiring the first and second derivatives of the polynomials to agree at those knots) and imposes the requirement of a linear relationship beyond the boundary knots, a constraint that has been shown to help address the potential for cubic splines to behave poorly in the tails of a distribution[12]. We used separate natural cubic splines according to diabetes status, and in each instance, we selected 1 interior knot and 2 boundary knots. The interior knot was placed at the median of the distribution of average glucose levels (101 mg/dL for participants without diabetes, 165 mg/dL for participants with diabetes), while the boundary knots were placed at the 10^{th} and 90^{th} percentiles (92 and 117 mg/dL for those without diabetes, 139 and 198 mg/dL for those with diabetes).

Results S1. Evaluation of influential observations.

We examined standardized delta-betas of the glucose level spline parameter estimates to identify potential influential observations. Standardized delta-betas illustrate the approximate change in regression coefficients (scaled by the standard error of the coefficients) that would result if an observation were deleted from the data. We plotted standardized delta-beta statistics for each included study participant for each of the four spline parameter estimates (two for the spline modeling glucose levels among those without diabetes and two for the spline for those with diabetes) for the dementia outcome. We identified the individuals with the most influence on these spline parameters and re-ran the primary analyses of associations between glucose levels and dementia omitting each of these individuals in turn. We visually inspected the spline curves and compared them with the spline curves from the primary analysis including all participants

Figure S3 shows the standardized delta-beta results. The x axis is a randomly generated participant number and is consistent across the two spline parameters for people without diabetes and people with diabetes (i.e. data from the same person are plotted in the same horizontal location). There were 1,835 people who did not have diabetes at the time they enrolled in the ACT study; their data are plotted in the top plots. There were 343 people who had diabetes at the end of our analyses, including 232 people who had diabetes at the time they enrolled in the ACT study, and 111 people who developed diabetes during the course of the study; their data are plotted in the bottom plots. The darkened circles indicate influential observations we evaluated further (see below).

For people without diabetes, we identified five people who had data that were relatively influential on at least one of the spline parameters. Three people had data that were relatively influential on the first spline parameter (top left panel); one had data that were relatively influential on the second spline parameter (top right panel); and one had data that were relatively influential on both spline parameters. There were no important differences in the primary results removing data from each of these individuals, however, which suggested that our results for people without diabetes were not particularly influenced by any influential observations.

For people with diabetes, we identified seven people as having data that were relatively influential on at least one of the spline parameters. Three had data that were relatively influential on the first spline parameter (bottom left panel); three had data that were relatively influential on the second spline parameter (bottom right panel); and one had data that were relatively influential on both spline parameters. We re-ran the primary analyses of the association between glucose levels and dementia, and found that data from three of these seven individuals had a notable effect on the shape of the spline curve.

Due to the influence of these three individuals on the overall results for people with diabetes, we considered data from these individuals carefully. We plotted their individual trajectories of glucose levels over time. These plots were helpful in understanding why they were influential on the overall study results, as all three had glucose levels during the time in which they were enrolled in the ACT study that were at the low extreme of the distribution (see Table S4 and Figure S1), i.e., much lower than typical for people with diabetes.

We obtained the medical records for these three individuals from Group Health and one of us (PKC) reviewed these charts with an eye toward the validity of the diabetes diagnosis. These three individuals with lower than typical glucose levels did not have well-established diagnoses of Type 2 diabetes. Two of these had isolated episodes of hyperglycemia that led to treatment with low-dose sulfonylurea therapy. One of these was on the initial starting dose for a few months and then discontinued; the other was on the initial starting dose for just over two years and then discontinued. Both of these individuals had excellent glucose levels for many years after their sulfonylurea was discontinued.

The third individual had an episode of hyperglycemia and was begun on sulfonylureas. This person had difficult to control glucose levels, and rapidly progressed to requiring insulin, soon requiring over 100 units of insulin daily. Subsequent evaluation led to the diagnosis of acromegaly, a growth hormone-producing pituitary tumor. This individual had surgical, radiation, and medical therapy for the pituitary tumor, after which their glucose levels returned to normal and they no longer required treatment for diabetes. Glucose levels were closely monitored for several years, and were not noted to be elevated again.

Our operational definition of diabetes was treatment with an antidiabetic medication. All three of these individuals had diabetes by that definition. However, they all had atypical natural histories of Type 2 diabetes.

Figure S4 shows the spline curve for the adjusted association between glucose levels and risk of dementia with data from the person who developed acromegaly removed.

This graph should be compared with the right panel in Figure 1 in the manuscript. The magnitude of the upwards trajectory to the left of this curve is somewhat lower than that shown in Figure 1. P values for the strength of association between glucose levels and risk of dementia were minimally affected by excluding data from this person; the p value was <0.01.

We further explored the effect of removing all three of the influential individuals with atypical natural histories of Type 2 diabetes. Figure S5 shows the spline curve for the adjusted association between glucose levels and risk of dementia with data from all three of these individuals removed.

This graph should also be compared with the right panel in Figure 1 in the manuscript. The magnitude of the upwards trajectory to the left of this curve is quite a bit lower than that shown in Figure 1. The p value for the strength of association between glucose levels and risk of dementia was <0.01.

Taken as a whole, these exploratory analyses suggested that our results for people without diabetes were not unduly influenced by data from any individual study participants. For people with diabetes, the three people whose data influenced the upward risk trajectory associated with lowest glucose levels each had atypical natural histories of Type 2 diabetes. More definitive data are certainly needed for people with diabetes, but overall our findings suggest that higher levels of glucose are associated with increased risk of dementia both among people with and people without diabetes.

Table S1. Baseline characteristics of ACT participants included in study and those excluded because of insufficient glucose or glycated hemoglobin measures at baseline.

	Included		Excluded	
	N	%*	N	%*
Total cohort	2,067		848	
Mean glucose level (mg/dL) over prior 5 years, median (25th, 75th)	102 (96, 113)			
Original study cohort enrolled 1994-1996	1,501	72.6	717	84.6
Age, median (25th, 75th)	75 (71, 81)		73 (69, 78)	
Female	1,228	59.4	507	59.8
Race, white	1,863	90.1	776	91.5
Education beyond high school	1,243	60.1	532	62.7
Apolipoprotein E ε4 allele†	461	25.4	186	23.7
Treated for diabetes	232	11.2	6	0.7
Atrial fibrillation	233	11.3	29	3.4
Ever treated for hypertension	1,437	69.5	295	34.8
Mean systolic blood pressure , median (25th, 75th)	139 (127, 156)		138 (126, 153)	
Mean diastolic blood pressure , median (25th, 75th) ‡	75 (68, 81)		76 (70, 83)	
Coronary artery disease§	510	24.8	68	8.0
Cerebrovascular disease¶	243	11.8	43	5.1
Congestive heart failure‖	104	5.0	11	1.3
Regular exercise**	1,462	70.7	613	72.4
Current smoker††	104	5.0	66	7.8
Former smoker††	978	47.3	358	42.2
Never smoker††	984	47.6	424	50.0
Fair or poor self-rated health	424	20.5	66	7.8

* Column percentages based on non-missing data.

† Missing in 249 included participants (11.2%) and 64 excluded participants (7.5%)

‡ Missing in 75 included participants (1.7%) and 7 excluded participants (0.8%)

§ Missing in 12 included participants (0.6%) and 0 excluded participants (0%)

¶ Missing in 12 included participants (0.6%) and 2 excluded participants (0.2%)

‖ Missing in 4 included participants (0.2%) and 0 excluded participants (0%)

** Missing in 0 included participants (0%) and 1 excluded participant (0.1%)

†† Missing in 1 included participant (0.0%) and 0 excluded participants (0%)

Table S2. Medications from Group Health pharmacy used to identify people treated for diabetes.	
Insulin	
Biguanides	
Metformin	
Meglitinides	
Nateglinide	Repaglinide
Sulfonylureas	
Acetohexamide	Glyburide
Chlorpropamide	Tolazamide
Glipizide	Tolbutamide
Thiazolidinediones	
Pioglitazone	Rosiglitazone

Table S3. Medications from Group Health pharmacy used to identify people treated for hypertension		
Angiotensin converting enzyme inhibitor		
Benazepril	Enalapril	Lisinopril
Captopril	Fosinopril	Ramipril
Angiotensin II receptor blockers		
Losartan	Valsartan	
Beta blockers		
Acebutolol	Labetalol	Propranolol
Atenolol	Metoprolol	Sotalol
Betaxolol	Nadolol	
Carvedilol	Pindolol	
Calcium channel blockers		
Amlodipine	Nicardipine	Verapamil
Diltiazem	Nifedipine	
Felodipine	Nimodipine	
Adrenergic – central		
Clonidine	Guanethidine	Methyldopa
Guanabenz	Guanfacine	
Adrenergic – peripheral		
Deserpidine	Prazosin	Terazosin
Doxazosin	Reserpine	
Peripheral vasodilators		
Hydralazine	Minoxidil	
Thiazide diuretics		
Chlorthalidone	Metolzone	Hydrochlorothiazide
Other diuretics		
Eplerenone	Spironolactone	Triamterene
Renin inhibitor		
Aliskiren		

Table S4. Exposure distribution of average glucose levels across study (based on 5 year windows prior to each dementia event)

Without diabetes		With diabetes	
Percentile	Value (mg/dL)	Percentile	Value (mg/dL)
0	78		
1	86		
5	90		
10	92		
25	96		
50	101	0	103
75	108		
90	117	1	121
95	125		
		5	130
		10	139
99	146	25	149
		50	165
		75	182
		90	198
		95	216
100	265	99	246
		100	292

Table S5. Causes of dementia*		
Type	**n**	**%**
Vascular	55	10%
Other medical	28	5%
Substance-induced	7	1%
Multiple etiologies	19	4%
Other or unknown cause	12	2%
Total, non-AD dementia cases	121	23%
NINCDS-ADRDA probable or possible AD	403	77%
Total, all-cause dementia cases	524	100%

* Two different summary variables are described in this table. First, we considered NINCDS-ADRDA criteria for probable or possible AD[13]. All participants with either probable or possible AD are shown in that row, regardless of their DSM-IV diagnosis. Other causes of dementia are based on DSM-IV criteria[14] for people who did not have probable or possible AD according to NINCDS-ADRDA criteria. This approach results in mutually exclusive categories for causes of dementia.

Table S6. Risk of incident dementia associated with recent (zero to five years prior) glucose levels among persons without and with diabetes, with additional adjustment of APOE genotype*

Without diabetes			**With diabetes**		
Average glucose level	HR	95% CI	**Average glucose level**	HR	95% CI
95 mg/dL	0.89	(0.78, 1.01)	150 mg/dL	1.06	(0.90, 1.25)
100 mg/dL	1.00	REF	160 mg/dL	1.00	REF
105 mg/dL	1.09	(1.01, 1.17)	170 mg/dL	1.04	(0.93, 1.15)
110 mg/dL	1.15	(1.04, 1.27)	180 mg/dL	1.18	(1.00, 1.40)
115 mg/dL	1.19	(1.05, 1.35)	190 mg/dL	1.44	(1.11, 1.86)
p-value	0.02		p-value	0.005	

* These models adjusted for the same covariates as in the primary analysis reported in Table 2 in the manuscript, with the addition of *APOE* genotype. P values represent results of omnibus tests (see note to Table 2).

Table S7. Risk of incident dementia associated with recent glucose levels defined as zero to two years (top) and zero to eight years (bottom) among people without and with diabetes.*

Without diabetes			With diabetes		
Average glucose level	HR	95% CI	**Average glucose level**	HR	95% CI
2 years: 95 mg/dL	0.92	(0.81, 1.04)	2 years: 150 mg/dL	1.14	(0.99, 1.30)
100 mg/dL	1.00	REF	160 mg/dL	1.00	REF
105 mg/dL	1.06	(0.99, 1.14)	170 mg/dL	0.98	(0.90, 1.06)
110 mg/dL	1.10	(0.99, 1.22)	180 mg/dL	1.05	(0.92, 1.20)
115 mg/dL	1.12	(0.98, 1.27)	190 mg/dL	1.21	(1.01, 1.46)
p-value	0.23		p-value	<0.001	
8 years: 95 mg/dL	0.83	(0.73, 0.94)	8 years: 150 mg/dL	1.07	(0.89, 1.29)
100 mg/dL	1.00	REF	160 mg/dL	1.00	REF
105 mg/dL	1.11	(1.04, 1.19)	170 mg/dL	1.03	(0.92, 1.15)
110 mg/dL	1.15	(1.04, 1.27)	180 mg/dL	1.18	(0.99, 1.40)
115 mg/dL	1.15	(1.00, 1.31)	190 mg/dL	1.44	(1.10, 1.87)
p-value	0.008		p-value	0.009	

* These models adjusted for the same covariates as in the primary analysis reported in Table 2 in the manuscript. The exposure window in the primary analyses was 5 years. This table presents results from 2-year exposure windows (top) and 8-year exposure windows (bottom). P values represent results of omnibus tests (see note to Table 2).

Table S8. Risk of incident dementia associated with recent glucose levels defined as zero to five years among people without and with diabetes, varying priors for the exposure model*

Without diabetes			With diabetes		
Average glucose level	HR	95% CI	**Average glucose level**	HR	95% CI
Model B: 95 mg/dL	0.79	(0.63, 0.97)	Model B: 150 mg/dL	1.15	(0.94, 1.40)
100 mg/dL	1.00	REF	160 mg/dL	1.00	REF
105 mg/dL	1.16	(1.03, 1.31)	170 mg/dL	0.99	(0.89, 1.11)
110 mg/dL	1.22	(1.06, 1.41)	180 mg/dL	1.13	(0.96, 1.34)
115 mg/dL	1.25	(1.05, 1.49)	190 mg/dL	1.41	(1.11, 1.80)
p-value	0.02		p-value	0.002	
Model C: 95 mg/dL	0.89	(0.82, 0.96)	Model C: 150 mg/dL	1.07	(0.91, 1.26)
100 mg/dL	1.00	REF	160 mg/dL	1.00	REF
105 mg/dL	1.08	(1.03, 1.14)	170 mg/dL	1.03	(0.93, 1.13)
110 mg/dL	1.13	(1.05, 1.22)	180 mg/dL	1.16	(1.00, 1.35)
115 mg/dL	1.15	(1.04, 1.28)	190 mg/dL	1.41	(1.13, 1.76)
p-value	0.006		p-value	0.002	
Model D: 95 mg/dL	0.82	(0.68, 1.00)	Model D: 150 mg/dL	1.13	(0.95, 1.34)
100 mg/dL	1.00	REF	160 mg/dL	1.00	REF
105 mg/dL	1.14	(1.01, 1.28)	170 mg/dL	1.00	(0.91, 1.11)
110 mg/dL	1.18	(1.01, 1.38)	180 mg/dL	1.14	(0.97, 1.33)
115 mg/dL	1.18	(0.99, 1.40)	190 mg/dL	1.40	(1.10, 1.78)
p-value	0.10		p-value	0.005	
Model E: 95 mg/dL	0.87	(0.78, 0.97)	Model E: 150 mg/dL	1.09	(0.93, 1.28)
100 mg/dL	1.00	REF	160 mg/dL	1.00	REF
105 mg/dL	1.09	(1.02, 1.17)	170 mg/dL	1.02	(0.93, 1.12)
110 mg/dL	1.13	(1.03, 1.25)	180 mg/dL	1.16	(0.99, 1.35)
115 mg/dL	1.14	(1.00, 1.28)	190 mg/dL	1.41	(1.11, 1.79)
p-value	0.03		p-value	0.01	

* These models adjusted for the same covariates as in the primary analysis reported in Table 2 in the manuscript. Models B through E refer to the specifications discussed in Supplemental Methods 4. P values represent results of omnibus tests (see note to Table 2).

Sensitivity 1 (Model B): Increase magnitude of variability but maintain relative magnitude of variability for glucose and HbA1c:

$\sigma_X^2 = (2*18.3)^2$ with diabetes; $\sigma_X^2 = (2*42.5)^2$ without diabetes; $\sigma_Y^2 = (2*15.7)^2$

Sensitivity 2 (Model C): Decrease magnitude of variability but maintain relative magnitude of variability for glucose and HbA1c:

$\sigma_X^2 = (0.5*18.3)^2$ with diabetes; $\sigma_X^2 = (0.5*42.5)^2$ without diabetes; $\sigma_Y^2 = (0.5*15.7)^2$

Sensitivity 3 (Model D): Increase magnitude of variability for measures based on glucose

$\sigma_X^2 = (2*18.3)^2$ with diabetes; $\sigma_X^2 = (2*42.5)^2$ without diabetes; $\sigma_Y^2 = 15.7^2$

Sensitivity 4 (Model E): Decrease magnitude of variability for measures based on HbA1c

$\sigma_X^2 = 18.3^2$ with diabetes; $\sigma_X^2 = 42.5^2$ without diabetes; $\sigma_Y^2 = (0.5*15.7)^2$

Table S9. Risk of incident dementia associated with recent glucose levels defined as zero to five years among people without and with diabetes, where average glucose level was defined to account for "fasting" laboratory values*****

Without diabetes			**With diabetes**		
Average glucose level	HR	95% CI	**Average glucose level**	HR	95% CI
95 mg/dL	0.90	(0.80, 1.00)	150 mg/dL	1.11	(0.94, 1.32)
100 mg/dL	1.00	REF	160 mg/dL	1.00	REF
105 mg/dL	1.09	(1.01, 1.17)	170 mg/dL	1.00	(0.90, 1.11)
110 mg/dL	1.14	(1.03, 1.27)	180 mg/dL	1.12	(0.95, 1.31)
115 mg/dL	1.17	(1.04, 1.33)	190 mg/dL	1.36	(1.09, 1.70)
p-value	0.04		p-value	0.002	

* These models adjusted for the same covariates as in the primary analysis reported in Table 2 in the manuscript. The only difference here is that the exposure model accounted for "fasting glucose" laboratory values, as outlined in Supplemental Methods 5. P values represent results of omnibus tests (see note to Table 2).

Figure S1. Distribution of glucose levels throughout the study period.

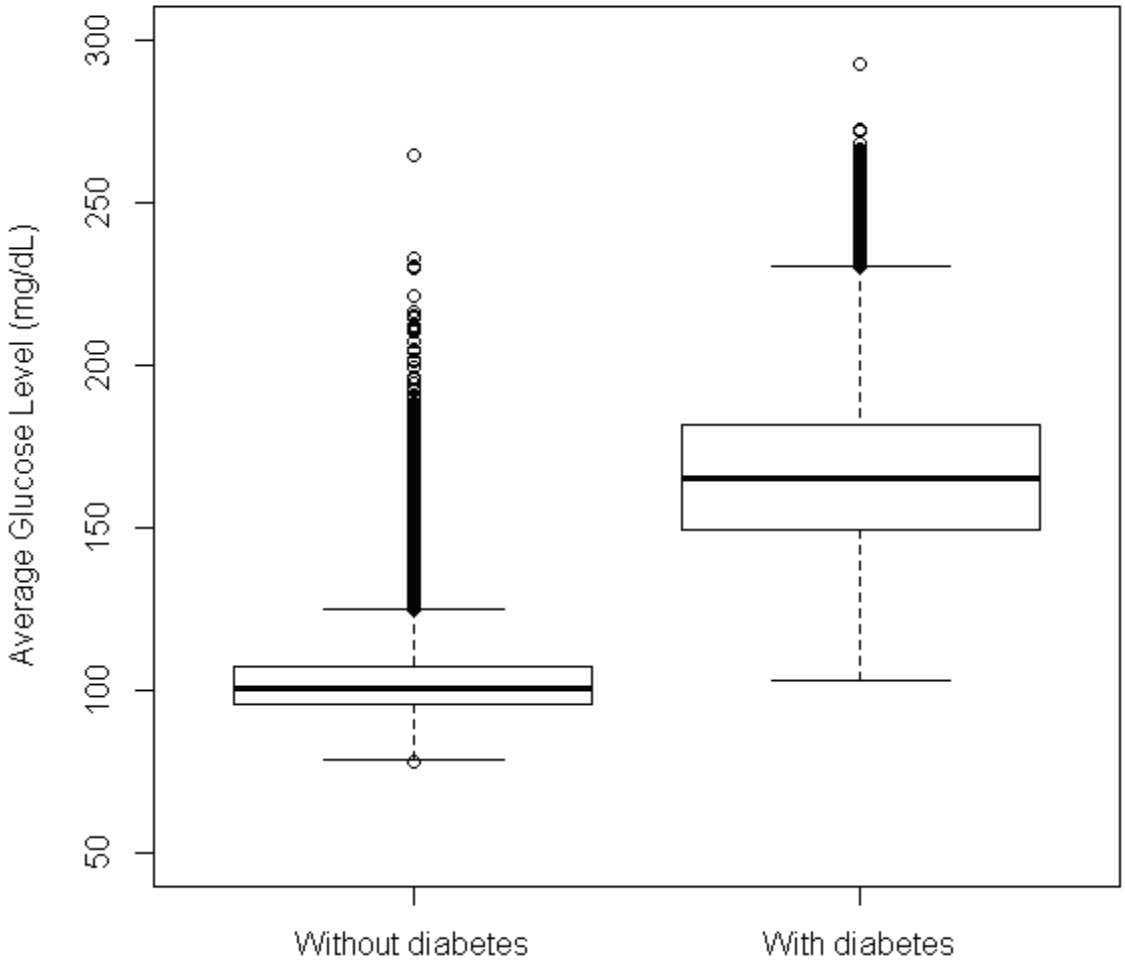
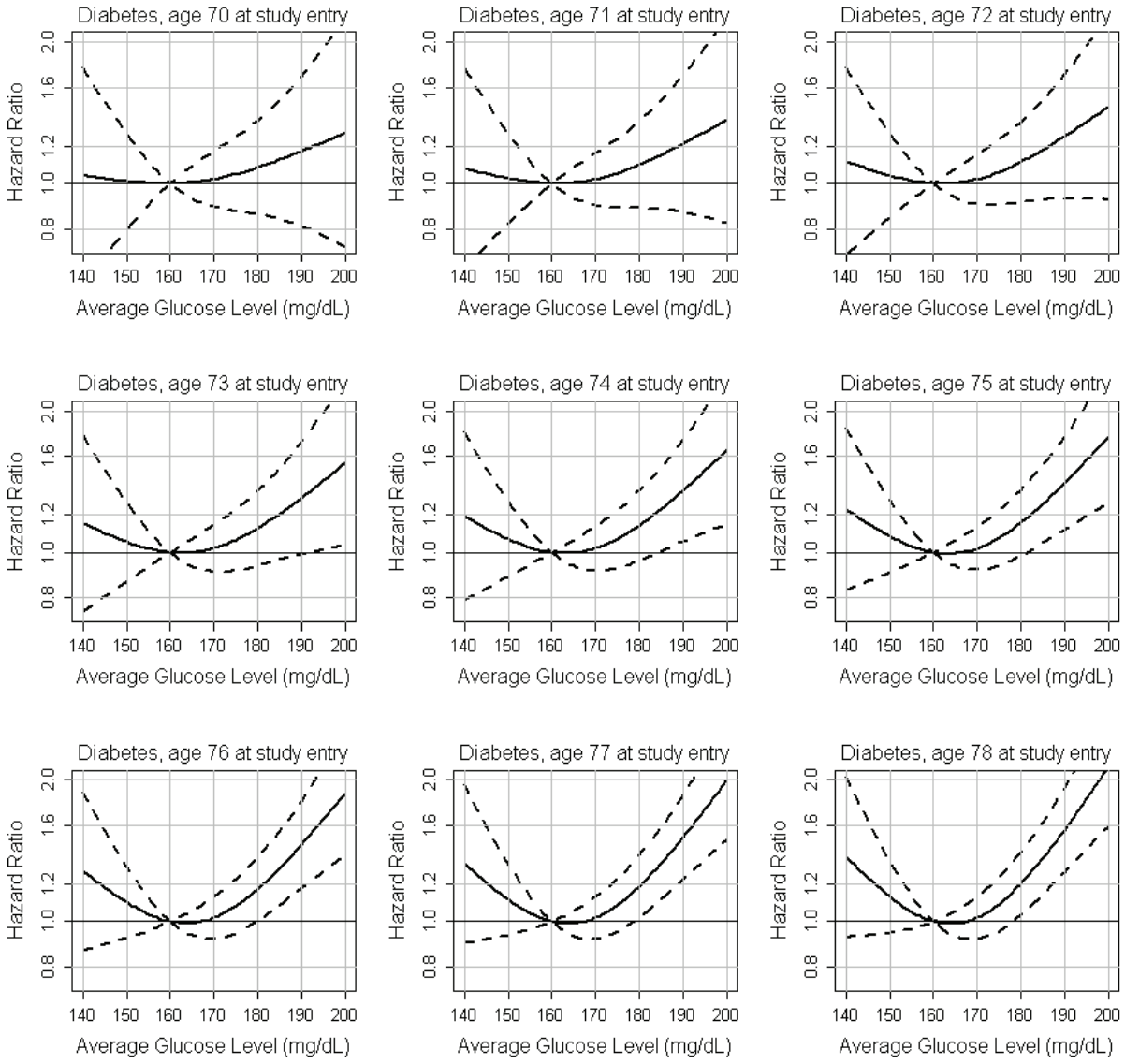


Figure S2. Evaluation of age at study entry among people with diabetes



This figure shows spline curves for the relationship between glucose levels and risk of dementia for participants with diabetes, stratified by age at study entry. Ages at study entry range from 70 in the top left panel to 78 at the bottom right panel (the inter-quartile range of age at study entry for people with diabetes). Higher risks associated with both higher and lower glucose levels appear to be especially prominent among people who were older at study entry. We performed these analyses for people with diabetes because of the suggestive p value for interaction terms between glucose level and age at study entry among people with diabetes (p=0.13).

Figure S3. Standardized delta-beta plots for the two spline parameters for people without diabetes (top panels) and with diabetes (bottom panels).

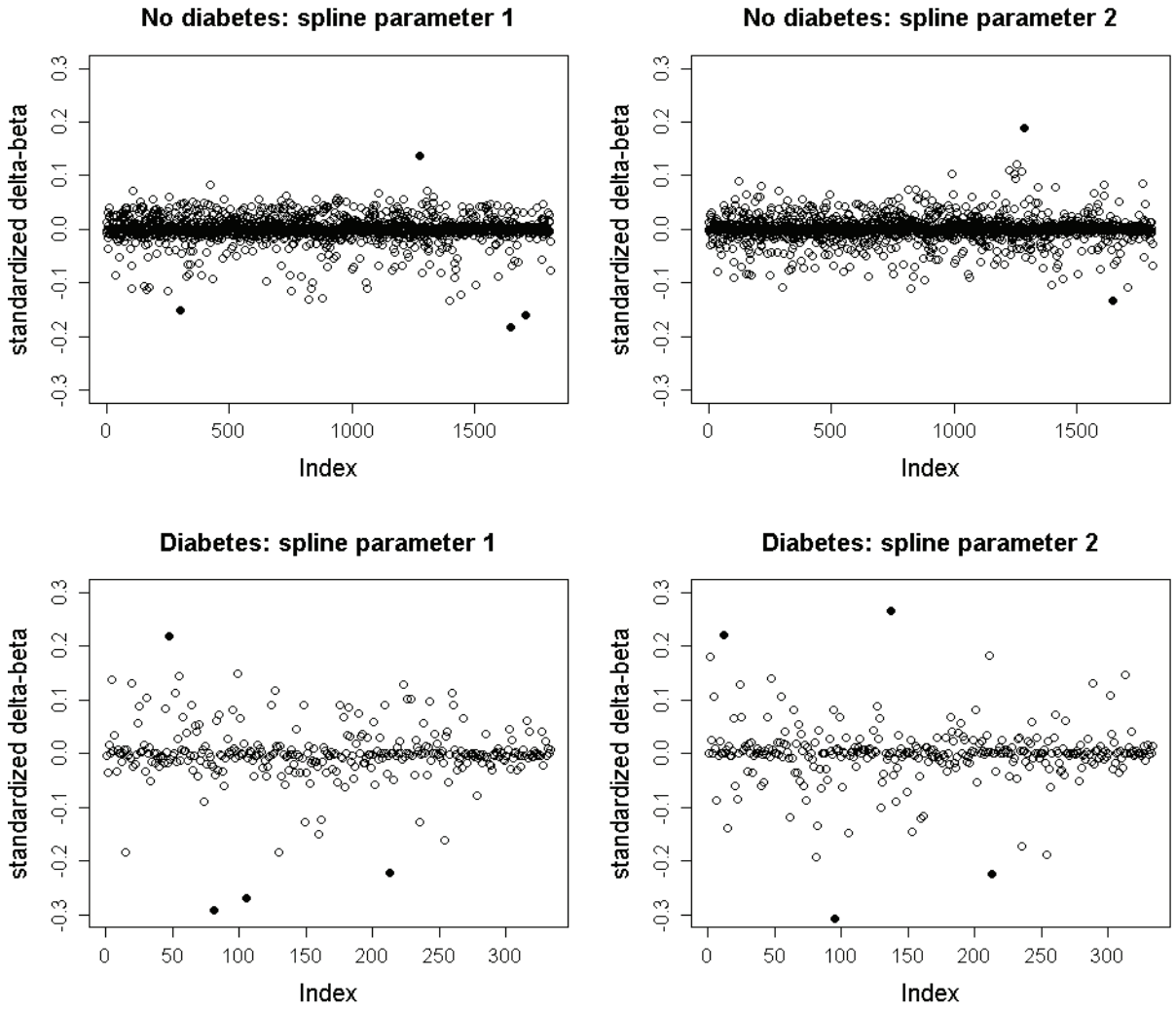


Figure S4. Association between glucose levels and dementia among people with diabetes after removing data from one individual with acromegaly

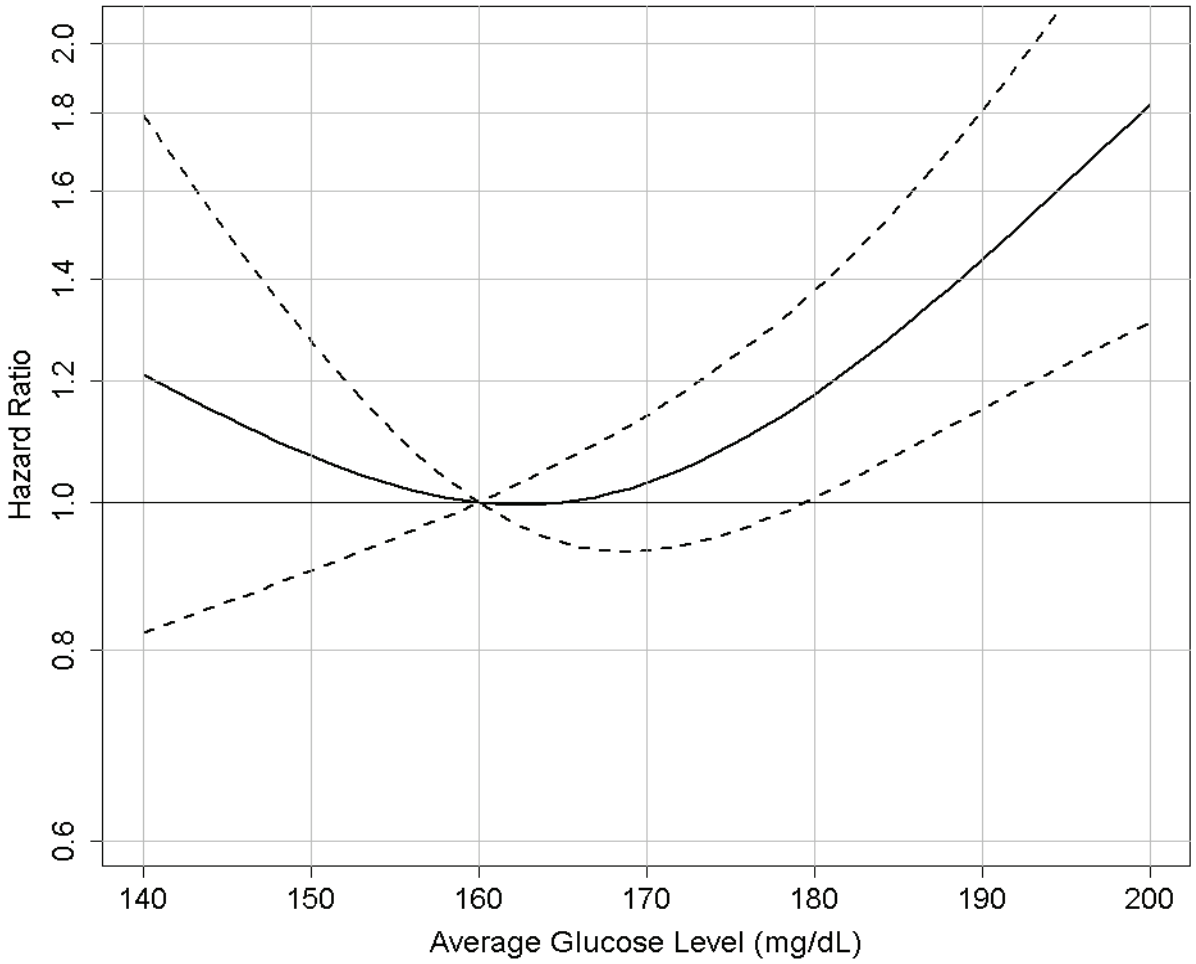


Figure S5. Association between glucose levels and dementia among people with diabetes after removing data from all three influential individuals who had atypical Type 2 diabetes natural histories.

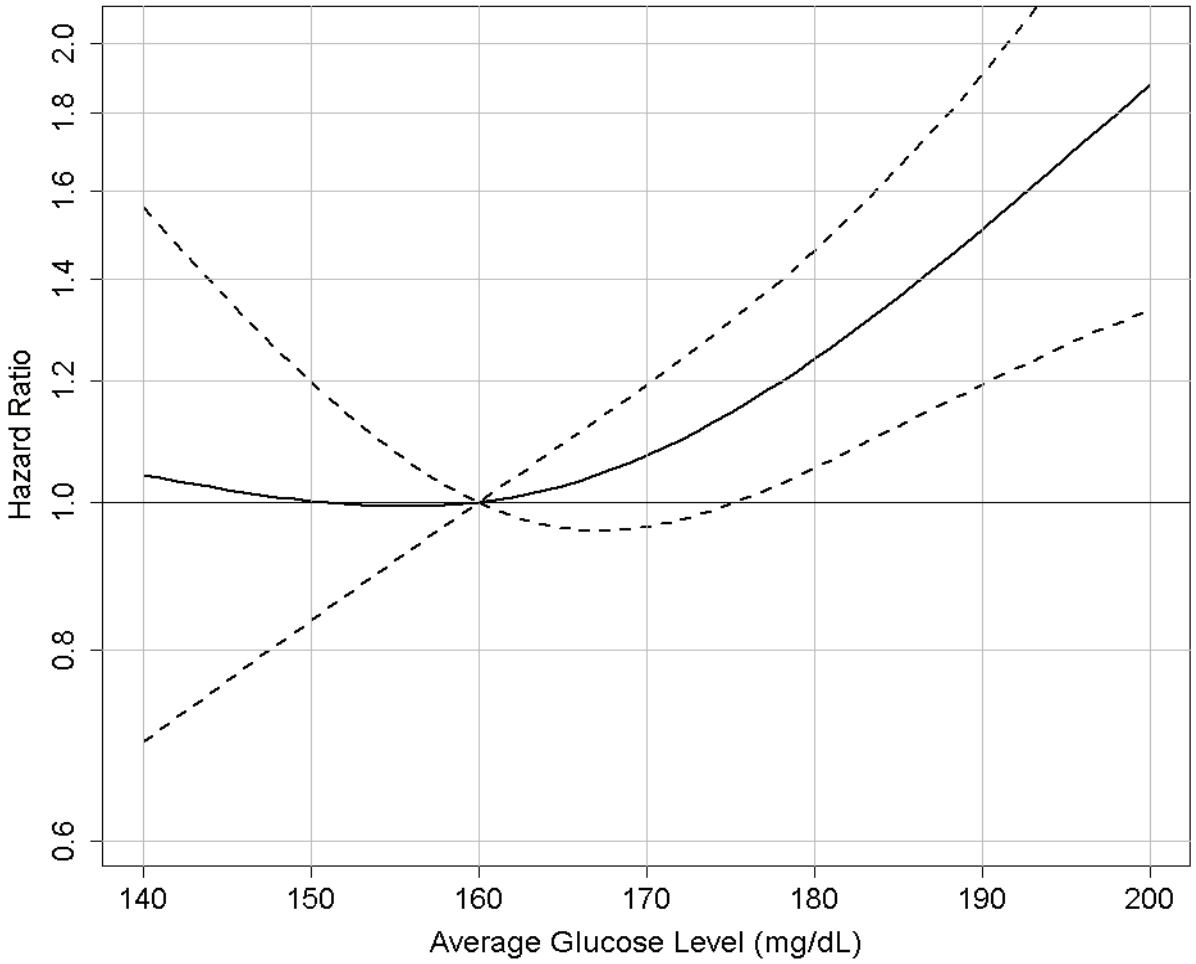
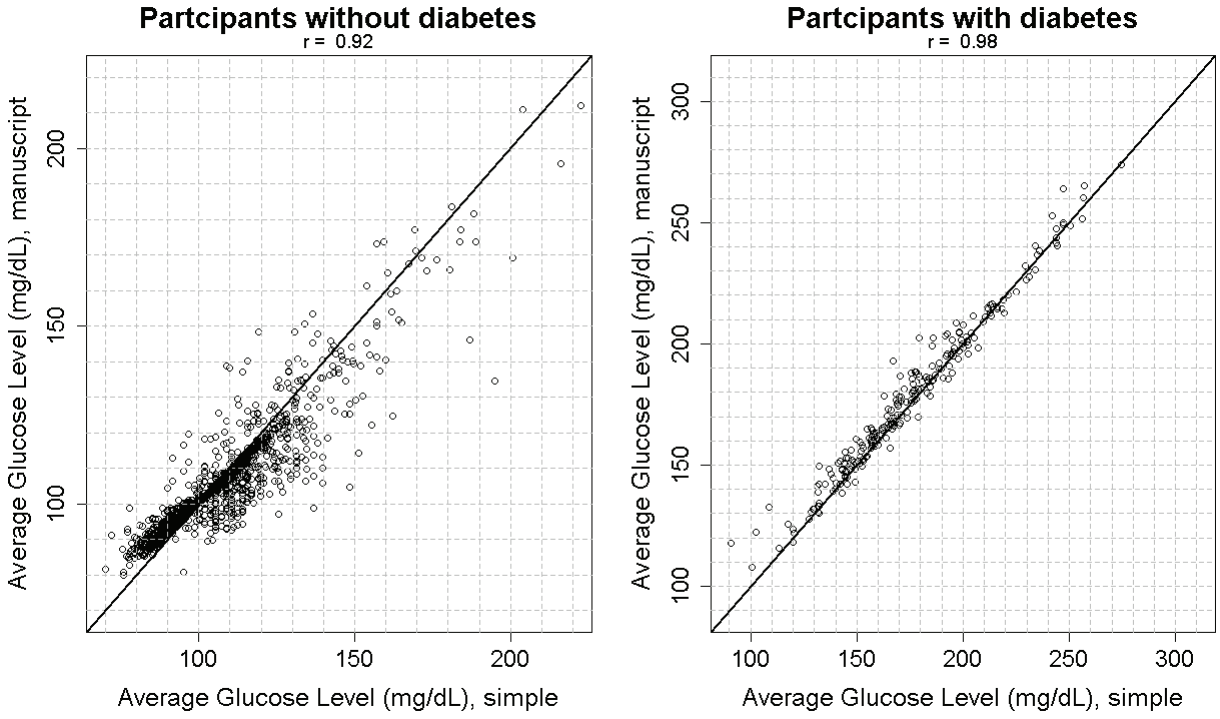


Figure S6. Scatter plot of glucose levels as used in the paper and using a simpler approach over the five years prior to study baseline for people without diabetes (left panel) and participants with diabetes (right panel)



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