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Association of fasting glucose with subclinical cerebrovascular disease in older adults without Type 2 diabetes

R. C. Sims[1], **L. I. Katzel**[2,3], **D. M. Lefkowitz**[4], **E.L. Siegel**[5], **W.F. Rosenberger**[6], **Z. Manukyan**[7], **K.E. Whitfield**[8], and **S.R. Waldstein**[2,3,9]

[1]School of Nursing, University of Delaware, Newark, DE

[2]Department of Medicine, Division of Gerontology and Geriatric Medicine, University of Maryland School of Medicine, MD

[3]Geriatric Research Education and Clinical Center, Baltimore Veterans Affairs Medical Center, Baltimore, MD

[4]Department of Diagnostic Radiology, University of Maryland School of Medicine, Baltimore County, USA

[5]Department of Diagnostic Radiology, Baltimore VA Medical Center, Baltimore County, USA

[6]Department of Statistics, George Mason University, Baltimore County, USA

[7]Biomed Idec, Baltimore County, USA

[8]Department of Psychology and Neuroscience, Duke University, Baltimore County, USA

[9]Department of Psychology, University of Maryland Baltimore County, USA

Abstract

Aims—To examine how fasting glucose and glucose tolerance are related to magnetic resonance imaging-assessed indicators of subclinical cerebrovascular disease and brain atrophy and their variation according to age, sex and education.

Methods—Participants in the present study were 172 healthy, community-dwelling older adults. An oral glucose tolerance test was administered and magnetic resonance imaging performed. Fasting, 2-h, and 2-h area-under-the-curve glucose levels, their associations with subclinical cerebrovascular disease and brain atrophy, and their respective interactions with age, sex and education were examined.

Results—A positive association between fasting glucose and subclinical cerebrovascular disease (but not brain atrophy) emerged; this association was more pronounced for participants with < 12 years of education; however, glucose tolerance was not related to subclinical cerebrovascular disease or brain atrophy.

Correspondence to: R. C. Sims. rsims@udel.edu.

Competing interests
None declared.

Conclusions—Findings revealed a potential link between fasting glucose levels and the presence of subclinical cerebrovascular disease indicators — white matter hyperintensities and silent brain infarction — in older adults without diabetes and with an education level below high school. Additional research is needed to confirm these associations and to determine the need for interventions aimed at closely monitoring and preventing elevated glucose levels in this population to reduce the prevalence of subclinical cerebrovascular disease.

Introduction

Subclinical cerebrovascular disease, characterized by silent brain infarction and white matter hyperintensities, and brain atrophy, characterized by ventricular enlargement and sulcal widening, are highly prevalent and significant public health concerns for older adults. Magnetic resonance imaging (MRI)-assessed silent brain infarcts were noted in 28% of stroke-free participants in the Cardiovascular Health Study (*n*=3647) and 20% of participants in the Rotterdam Scan Study (*n*=1077) [1, 2]. Global brain atrophy is also a common MRI finding among older adults [3]. Subclinical cerebrovascular disease and brain atrophy are predictive of incident cognitive decline [4], dementia [5] and stroke [6]. For example, in the prospective Rotterdam Scan Study, the presence of silent brain infarcts doubled the risk of dementia in participants free of dementia and stroke at baseline [6, 7]. Evidence of substantial subclinical cerebrovascular disease and brain atrophy has been noted among apparently healthy older adults [8, 9] and subclinical cerebrovascular disease and brain atrophy have further been associated with a number of cardiovascular risk factors. For example, within the Cardiovascular Health Study, white matter hyperintensities were associated with age, previous stroke, hypertension and the use of diuretics. In addition, ventricular enlargement and sulcal widening have been associated with previous stroke, hypertension, Type 2 diabetes and White race [9].

Type 2 diabetes has been implicated in a number of brain insults, including reduced grey matter volume, increased ventricle volume, and increased white matter lesion volume [10]. In addition, higher glucose levels within, and longer duration of Type 2 diabetes may work to exacerbate these changes [11]. As a particularly potent risk factor for MRI-assessed indicators of subclinical cerebrovascular disease (silent infarction and white matter hyperintensities) and brain atrophy (ventricular enlargement and sulcal widening), Type 2 diabetes has been linked specifically to the degree of white matter hyperintensities and brain atrophy in both cross-sectional and longitudinal studies [12, 13]. Given that 26.9% of US adults aged ≥65 years are currently diagnosed with Type 2 diabetes [14], associated neurological consequences are potentially common. Moreover, the prevalence of impaired fasting glucose and impaired glucose tolerance is high among older adults without Type 2 diabetes, with prevalence rates estimated at 39.1% for those aged ≥ 65 years (IFG), and 20.7% among individuals aged 60–74 years (IGT) [15]. Despite these alarming statistics, there are few studies examining the relationship of fasting glucose and glucose tolerance with MRI-assessed subclinical cerebrovascular disease and brain atrophy among older adults without Type 2 diabetes.

The association between fasting glucose, glucose tolerance and MRI outcomes may be influenced by several vulnerability and resilience factors including age, sex and education.

Given that greater age is a risk factor for Type 2 diabetes (26.9% of adults aged ≥ 65 years vs 11.3% of adults aged 20–64 years), it is plausible that age may interact with glucose to enhance vulnerability toward subclinical cerebrovascular disease and brain atrophy. Sex differences in the prevalence of Type 2 diabetes, by contrast, are nominal, with 11.8% of men aged ≥ 20 years affected vs 10.8% of women [14]; however, it is unknown whether the influence of fasting glucose and glucose tolerance on subclinical cerebrovascular disease and brain atrophy varies by sex. Finally, education may be an important resilience factor. According to the brain-reserve hypothesis, greater educational attainment may afford individuals a degree of protection against brain insult that is greater than for their counterparts with less education, and includes benefits such as preservation of brain volume, intensity of brain metabolism, connectivity in neural networks, efficiency of brain functioning, and enhanced protection against cognitive symptoms [16]. Consistent with this hypothesis, relations among fasting glucose, glucose tolerance and MRI outcomes may vary as a function of educational attainment, such that individuals with more education have fewer negative MRI outcomes, despite similar glucose profiles.

Examination of risk markers for Type 2 diabetes and MRI-based evidence of subclinical cerebrovascular disease and brain atrophy is critical for a full understanding of the role of glucose in the development of neuropathology. Understanding the role that specific demographic vulnerability and resilience factors may play in the development of glucose-related neuropathology is necessary to characterize these relationships more fully. Accordingly, the aim of the present study was to examine, in an exploratory cross-sectional analysis, the relationship of fasting glucose, 2-h glucose, and area-under-the-curve (AUC) glucose with MRI-assessed markers of subclinical cerebrovascular disease and brain atrophy in older adults without Type 2 diabetes, while assessing age, sex and education as potential effect modifiers.

Subjects and methods

Subjects

Healthy, community-dwelling older adults were recruited from the Baltimore Veterans Affairs Medical Center, the Geriatric Research Education and Clinical Center at the Baltimore Veterans Affairs Medical Center and through advertisement in the local community for a study of cardiovascular risk factors, neuroimaging and neurocognitive function [17]. Participants underwent multiple evaluations that included health history, a physical examination, blood chemistries, an oral glucose tolerance test, MRI and psychosocial and neuropsychological testing. Exclusion criteria included a previous diagnosis of cardiovascular disease (except mild to moderate hypertension), major medical disease, neurological disease, history of stroke or dementia, Mini-Mental State Examination score < 24 [18], psychiatric disorder, heavy alcohol use, use of medications affecting central nervous system function, and exercise-induced chest pain or silent myocardial ischaemia from an exercise electrocardiogram. All participants provided written informed consent in accordance with the institutional review boards at the University of Maryland, Baltimore and University of Maryland, Baltimore County.

Procedures

After an overnight fast, an antecubital intravenous catheter was inserted for blood sampling before oral ingestion of 75 g glucose. Samples were then obtained at 0, 30, 60, 90 and 120 min after ingestion of glucose. Plasma glucose levels were measured using the glucose oxidase method on a Beckman Glucose Analyzer (Beckman-Coulter Inc., Brea, CA, USA). AUC values were calculated using the trapezoidal rule. Fasting glucose, 2-h glucose and AUC values were examined separately in the statistical analyses.

The MRI was performed using a Phillips 1.5 Tesla scanner. The protocol consisted of sagittal T1 (TR/TE/thickness/matrix/field of view/averages = 465/14/6 mm/192X256/24/1), axial T1 (600/14/5 mm/192X256/23/2), dual contrast proton density/T2 (3500/16,96/5 mm/ 192x256/23/2), and fluid attenuated inversion recovery (FLAIR) (TR/TE/TI/thickness/ matrix/field of view/averages = 8000/120/2200/5 mm/192x256/21/2) sequences. Images were rated blindly for periventricular and deep white matter hyperintensities, number of silent infarctions, sulcal widening, and ventricular enlargement by a board-certified neuroradiologist (DML). Periventricular and deep white matter hyperintensities were rated using the method described by Fazekas *et al.* [19, 20]. Specifically, periventricular white matter hyperintensities were rated with the following coding scale: 0=absent; 1=cap; 2=band; and 3=irregular hyperintensity extending into the deep white matter. Deep white matter hyperintensities were rated as: 0=absent; 1=punctuate, limited; 2=beginning confluent; and 3=confluent. Silent brain infarction was coded using modified Cardiovascular Health Study criteria [1]; infarcts were defined as ≥3 mm in size. Brain atrophy was rated according to the apparent size of the ventricles (a measure of subcortical atrophy) and sulcal widening (an indication of cortical atrophy) using the following coding scale: 0=absent; 1=mild; 2=moderate; 3=severe.

Covariates

Covariates were selected based on known influence on MRI outcomes, inclusion in the relevant literature, and/or significant correlation in the present sample (lipid and smoking data were excluded for this reason). Age and education were assessed in years. Depressive symptomatology was assessed using the Beck Depression Inventory [21]. BMI was also calculated. Assessment of blood pressure was performed on two to three occasions with patients in a seated position using an automated vital signs monitor (Dinamap Model # 1846SX, Critikon, Tampa, FL, USA) and an appropriately sized occluding cuff. Blood pressure readings were averaged to yield an estimate of participants' resting systolic and diastolic blood pressure. Use of anti-hypertensive medications was collapsed into a single 'yes/no' category.

Statistical analysis

All statistical analyses were performed using SAS version 9.1 (Cary, NC, USA). All variables were assessed to ensure that they met the assumptions of the planned analyses (e.g. assumptions of normality). Principal components analysis, a data reduction technique, was run to reduce the number of MRI endpoints (periventricular white matter hyperintensities, deep white matter hyperintensities, silent brain infarction, ventricular enlargement and sulcal widening) for analysis. Principal components analysis is a statistical procedure that uses

orthogonal transformation to convert a set of observations of possibly correlated variables into a set of values of linearly uncorrelated variables called principal components. The first principal component that is derived has the largest possible variance, and each additional component has the highest variance possible under the constraint that it be orthogonal to (uncorrelated with) the preceding components. Principal components analysis yielded two MRI components with eigenvalues >1. Based on component loadings, the first component best represented subclinical cerebrovascular disease and included periventricular and deep white matter hyperintensities, and silent infarction. The second component best represented brain atrophy and included ventricular enlargement and sulcal widening. Because of the skewness and limited variability associated with the ordinal ratings (MRI data that were ranked), we transformed all MRI outcome variables using normal rank scores as follows (this transformation was necessary to meet assumptions of normality for subsequent regression analyses). First, we ranked the individual MRI outcome variables. Next, we transformed the rank scores to percentiles of a normal distribution, a procedure called 'normal scores transformation' [22]. We then added the transformed rank scores for periventricular and deep white matter hyperintensities and silent infarction to derive a 'rank sum score' reflecting the first brain component, subclinical cerebrovascular disease. The transformed rank scores for ventricular enlargement and sulcal widening were then added to derive a 'rank sum score' reflecting the second brain component, brain atrophy. Subsequent statistical examination of the distributions of these rank sum scores confirmed that the distributions had been normalized and were therefore appropriate to examine as outcome variables in multiple regression analyses.

To determine relations among fasting glucose, 2-h glucose, AUC and MRI components, multiple regression analyses were conducted for each MRI component for a total of six regressions. All outcomes were analysed as continuous variables. Within these models, interaction terms were created to assess the interactions of glucose variables with age, sex and education. Age and education were dichotomized in the following manner: age ≤70 years or >70 years (based on standard young–old/old–old age thresholds [23]); ≤12 or >12 years of education (less than a high school education vs high school education and higher). All models included the following covariates: age, education, sex, depression, BMI, systolic blood pressure and anti-hypertensive medications.

Results

Participant characteristics

The total number of participants who completed the parent study protocol was 207. Of the 207, only 179 completed MRI: 10 pilot participants were not invited to participate in MRI assessment, and 18 were excluded because of MRI contraindication (claustrophobia, metal in body) or scanner down time. Seven participants were excluded from the remaining 179 due to detection of clinical cardiovascular disease and/or fasting glucose levels >6.99 mmol/l. These exclusions resulted in a final sample size of 172 for the present data analyses. The mean (median; range) age of participants was 64.43 (65; 54–83) years and the mean (median; range) educational attainment was 16.25 (16; 8–24) years. The sample was 58% male and 87% White. Fourteen percent of the sample reported taking anti-hypertensive

medications. Twenty-one percent (*n*=44) of the sample met the criteria for impaired fasting glucose (≥ 5.55 and <6.99 mmol/l) and 25.5% (*n*=48) met the criteria for impaired glucose tolerance (2-h glucose ≥7.77 and <11.10 mmol/l). Just over 10% (*n*=18) of participants met the criteria for both impaired fasting glucose and impaired glucose tolerance. Fasting glucose values were in the normal range. Mean systolic blood pressure approached the pre-hypertensive range and BMI was in the overweight range. Depressive symptomatology in the sample was low. Sample characteristics can be found in Table 1.

Prevalence of MRI outcomes

Periventricular white matter hyperintensities were apparent in 87% of participants while deep white matter hyperintensities were noted in 74% of participants. Silent infarcts were apparent in 51% of participants. Evidence of ventricular enlargement and sulcal widening was apparent in 72 and 93% of participants, respectively.

Linear regression results

The relationships among fasting glucose, 2-h glucose, AUC and imaging outcomes, multiple regression analyses were conducted for each MRI endpoint, subclinical cerebrovascular disease and brain atrophy, for a total of six regressions. Linear regression results for the three subclinical cerebrovascular disease models are found in Table 2. Results for the three brain atrophy models are found in Table 3. After adjustment for all covariates, which included age, sex, education, depressive symptomatology, systolic blood pressure, BMI and anti-hypertensive medication use, fasting glucose showed a significant and positive linear association with subclinical cerebrovascular disease (β=4.752; *P*=0.011). Fasting glucose accounted for 3.7% of the variance in subclinical cerebrovascular disease. The fasting glucose × education interaction showed a significant association with subclinical cerebrovascular disease , such that higher levels of fasting glucose were predictive of greater subclinical cerebrovascular disease among participants with educational attainment < 12 years (β=−0.495; *P*=0.009). The fasting glucose × education interaction term explained 3.9% of the variance in subclinical cerebrovascular disease. This significant interaction was plotted, and illustrated the positive linear association between fasting glucose and subclinical cerebrovascular disease when education was lower, but a flat, nonsignificant association when education was higher. Results showed that when subclinical cerebrovascular disease was regressed on 2-h glucose and AUC glucose, no significant relations emerged. Similarly, no significant relations emerged when brain atrophy was regressed on fasting glucose, 2-h glucose and AUC glucose.

Discussion

The aim of the present study was to examine the relationship of fasting glucose and glucose tolerance with MRI-assessed markers of subclinical cerebrovascular disease (silent brain infarction and white matter hyperintensities) and brain atrophy (ventricular enlargement and sulcal widening) among older adults without Type 2 diabetes. Our findings revealed a significant association between fasting glucose and subclinical cerebrovascular disease that was education-dependent; only those with less than a high school education had greater subclinical cerebrovascular disease in the context of higher glucose levels; however, this

finding should be interpreted with caution, as the variance was of low clinical significance. It is also important to note that fasting glucose was not associated with brain atrophy. Moreover, 2-h glucose levels and AUC measures — indices of glucose tolerance — were not associated with the MRI endpoints. This respective pattern of findings is discussed below.

Previous research has demonstrated clear associations of Type 2 diabetes with subclinical cerebrovascular disease [12]. The present results suggest that fasting glucose levels and glucose tolerance have smaller and less consistent associations with subclinical cerebrovascular disease among older adults without diabetes. Precursors of Type 2 diabetes, such as impaired fasting glucose and impaired glucose tolerance, have previously been linked to poor health outcomes (cardiovascular disease) [24]. Our findings suggest the possibility that compromised cerebrovascular health may be initiated before the onset of frank diabetes as well. Various biological mechanisms that link metabolic disturbances such as elevated glucose and Type 2 diabetes to vascular changes may help to explain the present fasting glucose–subclinical cerebrovascular disease association and perhaps the prevalence of subclinical cerebrovascular disease in the sample. Research suggests various glucose-related disturbances may promote pathological changes in the arteries, including the large extracerebral arteries and the smaller, distal intracerebral arteries [25]. For example, within the metabolic syndrome, elevated fasting glucose levels are independently associated with subcortical white matter lesions and periventricular hyperintensities [26]. Ischaemia caused by microvascular occlusion and elevated erythrocyte aggregation may also play a role in glucose-related neuropathology [27]. Findings for Type 2 diabetes suggest that elevated glucose levels increase blood–brain barrier permeability, potentially allowing the passage of toxic substances [28]. Development of advanced glycosylated end products, that are commonly associated with Alzheimer’s disease pathology (senile plaques and neurofibrillary tangles) have been linked to chronic hyperglycaemia [29]. Furthermore, hyperglycaemia has been tied to increased aldose reactivity that may have a negative impact on neuronal functions [29]. It is possible that these explanatory mechanisms encompass early-stage cerebrovascular disease. While we cannot determine conclusively from our exploratory analysis if elevated fasting glucose levels are directly toxic or form a biomarker for other processes that cause subclinical cerebrovascular disease , longitudinal research may help to disentangle the potential mechanisms responsible for glucose-related subclinical cerebrovascular disease progression over time. Based on the high level of impaired fasting glucose in the older adult population [14, 15], the implications of an association between fasting glucose levels and subclinical cerebrovascular disease may suggest a major public health concern. To the extent that future studies may demonstrate that fasting glucose levels precipitate subclinical cerebrovascular disease before progression to Type 2 diabetes, a large percentage of older adults may be at risk for, or already display evidence of, subclinical cerebrovascular disease . In addition, as the epidemic of obesity increases impaired fasting glucose rates and affects all cross-sections of the population, the prevalence of subclinical cerebrovascular disease is likely to increase. The resulting consequences of subclinical cerebrovascular disease for neurocognitive function among a large percentage of older adults may be far-reaching.

Whereas fasting glucose had a small association with subclinical cerebrovascular disease, glucose tolerance did not. Their distinguishing features may help to explain this difference. Both impaired fasting glucose and impaired glucose tolerance represent early metabolic abnormalities that precede Type 2 diabetes; however, these markers are distinctive. The major difference lies within the site of insulin resistance [30]. Individuals with isolated impaired fasting glucose mainly have hepatic insulin resistance and normal muscle insulin resistance, whereas individuals with isolated impaired glucose tolerance have normal to slightly reduced hepatic insulin resistance and moderate to severe muscle insulin resistance [30]. If the pattern of findings for the sample indeed reflect patterns that are found in individuals with impaired fasting glucose and impaired glucose tolerance, it is possible that the hepatic site of insulin resistance may pose more of a risk for subclinical cerebrovascular disease than the muscle site of insulin resistance; however, additional research in older adults with one or other of these conditions is necessary to test this inference.

The interaction of fasting glucose and education noted in the present study suggests that higher levels of education may offer a buffering effect against the pathological impact of glucose on subclinical cerebrovascular disease among older adults without Type 2 diabetes. In that regard, the distinction between having graduated from high school or not should be further explored as a meaningful threshold with regard to fasting glucose and subclinical cerebrovascular disease. Subsequent glucose × education hypotheses may be tested in the context of the brain-reserve hypothesis that suggests greater educational attainment may protect against the progression of neuropathology and associated neurocognitive symptoms [16]. Importantly, we did not directly test this hypothesis, but future research may consider this possibility. Regardless, whereas age and sex did not represent significant vulnerability or resilience factors, education represented a potentially modifiable resilience factor for subclinical cerebrovascular disease. Longitudinal research is needed to confirm these inferences.

No significant results emerged to indicate that our sample had brain atrophy related to fasting glucose or glucose tolerance levels. Evidence from previous reports suggests that Type 2 diabetes is associated with brain atrophy [12, 13]; however, there were no significant associations between glucose variables and brain atrophy in this sample. It is possible that a specific threshold value or range of fasting glucose values among individuals without Type 2 diabetes is necessary to precipitate brain atrophy, or that there are non-linear effects of fasting glucose on brain atrophy that were not captured in the present analysis. Another explanation for the nonsignificant brain atrophy findings may be that the progression of neurological changes associated with elevated fasting glucose among participants is one that is more strongly associated with white matter disease and infarction, rather than brain atrophy. Further research is needed to delineate the specific consequences, pathways, and rates of neurological change associated with fasting glucose in this population.

Interestingly, variables with a known association with subclinical cerebrovascular disease and brain atrophy — age, systolic blood pressure and BMI — were not related independently to these endpoints in the present analyses. These nonsignificant findings may reflect the restricted range of age and systolic blood pressure (by design) and BMI in this sample, in addition to their shared variance with the glucose variables. The healthiness of

the sample, coupled with their relatively high level of educational attainment, may also explain the lack of association between age and MRI outcomes. Non-significant associations for sex were not unexpected, given that there are no significant sex differences in the prevalence of Type 2 diabetes in the general population.

The present study has several limitations. First, the reported associations should be treated with caution as the number of regressions that were run increased the likelihood of a Type 1 error; however, the pattern of results suggests initial trends for an understudied research topic, and appears to be non-random and parallel to other documented findings. Next, given the cross-sectional design and fluctuating nature of fasting glucose and glucose tolerance values, it is possible that data collection on a subsequent day may have yielded different results. We cannot ensure the directionality of the findings; it is possible that subclinical cerebrovascular disease may precede elevated fasting glucose. Longitudinal studies are needed to confirm the temporal relations of our findings. Another limitation is the use of years of education as a proxy for cognitive reserve. Other measures of crystallized intelligence might serve as more accurate proxies, such as measures of verbal IQ. As with the majority of aging studies, a healthy survivor effect may explain some of our nonsignificant findings. Finally, the relatively small size and predominately White ethnic background of the sample limit the generalizability of the findings.

In conclusion, our findings suggest that further examination of glucose levels in people without diabetes and MRI outcomes is warranted. A study sample that meets the criteria for impaired fasting glucose and impaired glucose tolerance may provide better evidence of an association between glucose and subclinical cerebrovascular disease and help to elucidate the progression of the neurological changes associated with glucose levels in older adults without diabetes. The presence of a small fasting glucose--subclinical cerebrovascular disease association in the absence of Type 2 diabetes suggests that the modest goal of preventing older adults from progressing from impaired fasting glucose or impaired glucose tolerance to Type 2 diabetes may not be sufficient. Indeed this may have implications for public health as millions are overweight or obese, have impaired fasting glucose and/or impaired glucose tolerance, and are projected to develop Type 2 diabetes. Accordingly, targeted interventions may help to prevent elevated glucose levels and reduce the risk of developing cerebrovascular disease. Interventions that promote close monitoring of glucose levels, regular physical activity, and adherence to a healthy dietary pattern (such as the Mediterranean diet) may play a role in reducing this risk.

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What's new?

- The present study finds that minimally elevated fasting glucose levels may enhance the progression of subclinical cerebrovascular disease in older adults without Type 2 diabetes.
- Education may play a role in buffering the effects of elevated glucose levels on the development of subclinical cerebrovascular disease.
- Glucose levels should be monitored carefully by older adults without Type 2 diabetes because of the documented impact of subclinical hyperglycaemia on brain outcomes.

Table 1

Sample characteristics (*N*=172)

Characteristic	Value
Mean (SD; range) age, years	64.43 (13.09; 54–83)
Mean (SD; range) education, years	16.25 (2.86; 8–24)
Male gender, *n* (%)	99 (58)
White race, *n* (%)	152 (88)
Use of anti-hypertensive medications, *n* (%)	37 (14)
Impaired fasting glucose* *n* (%)	44 (21)
Impaired glucose tolerance†, *n* (%)	48 (25.5)
Both impaired fasting glucose and inpaired glucose tolerance, *n* (%)	18 (10.4)
Mean (SD; range) fasting glucose, mmol/l	5.23 (0.49; 4.16–6.82)
Mean (SD; range) 30-min glucose, mmol/l	8.19 (1.42; 5.11–13.54)
Mean (SD; range) 1-h glucose, mmol/l	9.01 (2.45; 3.44–16.65)
Mean (SD; range) 90-min glucose, mmol/l	8.24 (2.74; 3.77–18.87)
Mean (SD; range) 2-h glucose, mmol/l	7.38 (2.53; 3.16–20.59)
Mean (SD; range) Beck Depression Inventory total score	3.71 (4.21; 0–23)
Mean (SD; range) BMI, kg/m^2	27.68 (4.78; 17.83–42.50)
Mean (SD; range) systolic blood pressure, mmHg	128.77 (16.97; 95–178)
Mean (SD; range) diastolic blood pressure, mmHg	73.59 (8.93; 50–102)
Mean (SD; range) total cholesterol, mmol/l	5.06 (0.82; 2.56–8.62)
Mean (SD; range) LDL cholesterol, mmol/l	3.13 (0.70; 1.09–6.67)
Mean (SD; range) HDL cholesterol, mmol/l	1.36 (0.42; 0.65–2.82)
Mean (SD; range) triglycerides, mmol/l	1.26 (0.62; 0.33–5.49)

* ≥5.55 and <6.99 mmol/l;

† ≥7.77 and <11.10 mmol/l.

Table 2

Linear multiple regression: fasting glucose, 2-h glucose, area-under-the-curve glucose, covariates, and interactions predicting subclinical cerebrovascular disease (*N*=172)

	Standardized β	*P*	Adjusted R^2
Fasting glucose	4.752*	0.011	0.037
Age	0.141	0.584	0.002
Education	−0.258*	0.010	0.038
Sex	0.128	0.590	0.002
Beck Depression Inventory score	0.065	0.018	0.033
Systolic blood pressure	−0.007	0.306	0.006
BMI	−0.007	0.778	<0.001
Anti-hypertensive medication	0.047	0.856	<0.001
Fasting glucose × age	0.090	0.848	<0.001
Fasting glucose × education	−4.95**	0.009	0.039
Fasting glucose × sex	−0.306	0.500	0.003
2-h glucose	0.108	0.664	0.001
Age	0.052	0.543	0.002
Education	−0.092	0.962	<0.001
Sex	0.050	0.510	0.003
Beck Depression Inventory	0.056	0.047	0.023
Systolic blood pressure	<0.001	0.982	<0.001
BMI	−0.012	0.632	0.001
Anti-hypertensive medication	0.048	0.850	<0.001
2-h glucose × age	0.018	0.871	0.001
2-h glucose × education	−0.036	0.217	<0.001
2-h glucose × sex	−0.126	0.850	0.009
AUC glucose	0.018	0.401	0.004
Age	0.806	0.530	0.002
Education	1.386	0.661	0.001
Sex	0.571	0.609	0.001
Beck Depression Inventory	0.059	0.038	0.026
Systolic blood pressure	<0.001	0.888	<0.001
BMI	−0.016	0.517	0.002
Anti-hypertensive medication	0.052	0.839	<0.001
AUC glucose×age	−0.018	0.890	<0.001
AUC glucose×education	−0.108	0.558	0.002
AUC glucose×sex	−0.054	0.375	0.005

* Significant at $P < 0.05$;

** significant at $P<0.01$. AUC, area-under-the-curve.

Table 3

Linear multiple regression: fasting glucose, 2-h glucose, area-under-the-curve glucose, covariates, and interactions predicting brain atrophy (*N*=172)

	Standardized β	*P*	Adjusted R^2
Fasting glucose	1.314	0.331	0.004
Age	−0.288	0.859	0.001
Education	7.361	0.289	0.005
Sex	1.600	0.317	0.005
Beck Depression Inventory	0.011	0.569	0.002
Systolic blood pressure	−0.001	0.337	0.004
BMI	0.007	0.706	0.001
Anti-hypertensive medication	−0.195	0.284	0.005
Fasting glucose × age	0.252	0.406	0.003
Fasting glucose × education	−1.422	0.475	0.006
Fasting glucose × sex	0.216	0.277	0.002
2-h glucose	−0.054	0.716	0.001
Age	0.615	0.299	0.005
Education	−0.744	0.578	0.001
Sex	0.535	0.307	0.005
Beck Depression Inventory	0.011	0.581	0.001
Systolic blood pressure	−0.001	0.234	0.007
BMI	0.001	0.974	0.001
Anti-hypertensive medication	−0.177	0.318	0.005
2-h glucose × age	0.054	0.448	0.003
2-h glucose × education	−0.108	0.640	0.001
2-h glucose × sex	0.072	0.867	0.001
AUC glucose	−0.018	0.868	0.001
Age	0.254	0.775	0.001
Education	−0.674	0.758	0.001
Sex	0.345	0.655	0.001
Beck Depression Inventory	0.011	0.567	0.002
Systolic blood pressure	−0.001	0.240	0.007
BMI	−0.0001	0.987	0.001
Anti-hypertensive medication	−0.167	0.347	0.004
AUC glucose × age	0.036	0.369	0.004
AUC glucose × education	0.036	0.916	0.001
AUC glucose × sex	0.002	0.816	0.0001

AUC, area-under-the-curve.