

# Opposite associations of aortic aneurysm with blood glucose and with diabetes

Morris - Blood glucose, diabetes & aortic aneurysm

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**Word count:** 794 words

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The prevalence of aortic aneurysm is inversely associated with the prevalence of diabetes, but the reasons for this inverse relationship remain unclear.<sup>1</sup> The two main hypotheses to explain it are: (I) high blood glucose, or some other aspect of diabetes, has a direct fibrotic or other effect on the aortic wall that inhibits aneurysm development (in which case pre-diabetes could well have a protective effect); or (II) some common diabetes treatment protects against aneurysm development.<sup>1</sup> These hypotheses predict different relationships of pre-diabetes to aneurysm development, yet no large studies have assessed the associations of blood glucose with subclinical aortic aneurysm among people without diabetes. The aim of this study was to assess the associations of blood glucose with screen-detected aortic aneurysm in a large population of otherwise healthy adults without diabetes.

The population comprised self-referred adults who attended commercial vascular screening clinics in the UK/USA during 2008-13. They underwent ultrasound screening for aortic aneurysm, carotid stenosis and peripheral artery disease. Diabetes was defined by previous diagnosis and/or antihyperglycemic treatment. Blood glucose was measured in capillary blood samples at point-of-care (Cholestech LDX®) using the oxidase/peroxidase method,<sup>2</sup> of which over 90% were fasting samples. The LDX method has a mean bias of -0.8 mmol/L (SD 0.6) and a percentage bias of -17.6% (SD 13.4) for the measurement of blood glucose compared with standard methods.<sup>2</sup> Vascular screening was conducted using dedicated vascular ultrasound instruments (GE LOGIQ e®). Aortic aneurysm was defined as a maximum infra-renal aortic diameter  $\geq 3$ cm. Analyses were restricted to findings at first screening examination, and, to minimize the influence of reverse causation, excluded participants who reported a previous diagnosis of ischemic heart disease, stroke,

transient cerebral ischemia, peripheral artery disease or aortic aneurysm. Participants were not representative of the general population, but this should not materially bias any associations between screen-detected arterial lesions and either diabetes or blood glucose.

Multivariable logistic regression was used to assess the associations of blood glucose (among people without diagnosed diabetes) and of diabetes itself (in the entire population) with screen-detected vascular disease. Analyses were adjusted for age, sex, BMI group, systolic blood pressure, smoking, and region; and for the use of aspirin, antihypertensive and low density lipoprotein-cholesterol lowering therapy.. Odds ratios in four categories defined by blood glucose measurements at the first screening invitation were plotted against the usual blood glucose levels in those categories (i.e., the mean glucose values including the first re-survey measurement; to correct for regression dilution).<sup>3</sup> The results are therefore referred to in terms of 'usual' blood glucose differences, as opposed to differences in baseline blood glucose levels that may underestimate the magnitude of risk factor associations. The University of Oxford Inter-Divisional Research Ethics Committee approved the study. Attendees provided written consent to the collecting organisation for research use of deidentified data.

Among 3,276,139 people screened in 2008-13, 2,065,432 (63%) were eligible and included in the analysis. 98% were from the USA, mean age was 64 (SD 10) years, and two-thirds were women. Approximately 11% (224,840) had a prior diagnosis of diabetes, and most of those reported current antihyperglycemic treatment (84%; 43,200 of 51,550 who were asked). Blood glucose measurements were available for 396,023 attendees, including 29,919 with diagnosed diabetes and 366,104 without (of

whom 344 had a resurvey). Those with diagnosed diabetes had a mean blood glucose of 6.9 mmol/L (SD 2.8), compared with 5.0 mmol/L (SD 1.0) among those without.

Diabetes was associated with about 50% higher prevalence of carotid stenosis (odds ratio 1.45, 95%CI 1.40-1.50;  $p<0.0001$ ) and peripheral artery disease (1.53, 1.49-1.57;  $p<0.0001$ ). In contrast, diabetes was associated with a 22% lower prevalence of aortic aneurysm (0.78, 0.74-0.83;  $p<0.0001$ ). Yet, among people without diagnosed diabetes, higher blood glucose was significantly positively associated with a higher prevalence of all three of these screen-detected vascular conditions, including aortic aneurysm. Each 2 mmol/L higher usual blood glucose was associated with a higher prevalence of carotid stenosis (odds ratio 1.36, 1.23-1.51;  $p<0.0001$ ), peripheral artery disease (1.36, 1.26-1.47;  $p<0.0001$ ) and aortic aneurysm (1.22, 1.04-1.43;  $p=0.017$ ).

The Figure shows that for both carotid stenosis and peripheral artery disease, prevalence was higher with higher usual blood glucose, and was highest among those with diabetes. It also shows, however, that although the prevalence of aortic aneurysm was higher with higher blood glucose in the non-diabetic range, the lowest prevalence was among people who had diabetes. The results were unchanged after restricting blood glucose measurements to fasting samples.

In conclusion, among people without diabetes, increased blood glucose levels were positively associated with higher prevalence of aortic aneurysm. These findings make it unlikely that the inverse association between diabetes and aortic aneurysm is mediated by hypothetical protective effects of glycemia or of other metabolic aspects

114 of diabetes. Instead, some common treatment for diabetes may well have a protective  
115 effect against aortic aneurysm.

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## **Acknowledgements**

The authors acknowledge Joelle Reizes, Mohsen Chabok, and Andrew Manganaro (Life Line Screening) and Steven Weisman (Innovative Science Solutions) who facilitated this research.

## **Source of Funding**

This study was supported by core funding to the MRC Population Health Research Unit, which receives direct support from the British Heart Foundation (BHF) and Cancer Research UK. DM is supported by a General Sir John Monash Scholarship and an Avant Doctor in Training Research Scholarship. DP is supported by a BHF Centre of Research Excellence Senior Transition Fellowship [RE/13/1/30181]. AH is supported by the UK Health Research (NIHR) Oxford Biomedical Research Centre (BRC). SL and RB are supported by the Medical Research Council of the UK, and a Goodger and Schorstein Scholarship from the University of Oxford Medical Sciences Division.

## **Disclosures**

The authors declare no conflicts of interest. Data were analyzed and interpreted by the investigators independently of Life Line Screening and all funding sources.

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## **Figure Legend**

### **Figure. Associations of usual blood glucose with three screen-detected vascular diseases**

Odds ratios are adjusted for age, sex, region, body-mass index group, systolic blood pressure, and smoking; and use of aspirin, antihypertensive therapy and low density lipoprotein-cholesterol lowering therapy, and are scaled so that the odds ratios for those with diabetes are compared against those without diabetes. Black squares: people without diabetes, plotted against the means of the resurvey glucose values. Quartiles defined by equal numbers of cases in each group. White squares: previously diagnosed diabetes or antihyperglycemic treatment, plotted against the mean blood glucose (of those who had it measured). In each group, the number of cases is given and the area of the square is inversely proportional to the variance of the log odds in that group.