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ARTICLE

Serum albumin concentration and incident type 2 diabetes risk: new findings from a population-based cohort study

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Abstract
Aims/hypothesis Serum albumin concentrations may be associated with future risk of type 2 diabetes, but the epidemiological evidence is limited and uncertain. We prospectively assessed the association between baseline values of serum albumin and incident type 2 diabetes risk in the Kuopio Ischaemic Heart Disease population-based cohort study.
Methods We analysed the data of 1,785 men aged 42–61 years with no known history of diabetes at baseline. Participants' serum albumin concentrations were measured at baseline. HRs and 95% CIs for type 2 diabetes events were subsequently assessed.
Results During a mean follow-up of 20.4 years, 382 participants developed diabetes. Serum albumin concentrations were weakly correlated with several established risk factors for diabetes. Serum albumin was approximately linearly associated with type 2 diabetes risk. In analyses adjusted for several conventional risk factors, the HR for type 2 diabetes per 1 SD increase in serum albumin was 1.15 (95% CI 1.03, 1.28; p=0.016), which persisted after further adjustment for triacylglycerol, C-reactive protein, γ-glutamyltransferase, estimated glomerular filtration rate and total energy intake (HR 1.15; 95% CI 1.02, 1.29; p=0.018). The findings were generally consistent across several clinical subgroups. Addition of information on serum albumin to a diabetes risk prediction model containing conventional risk factors led to no significant change in C-index (0.0126; 95% CI −0.0055, 0.0306; p=0.17).
Conclusions/interpretation A near linear, positive and independent association was found between serum albumin and type 2 diabetes, but this did not improve event discrimination. Further work is warranted to evaluate the causal relevance of these findings.

Keywords Risk factor · Serum albumin · Type 2 diabetes

Abbreviations

BCP	Coulter's bromcresol purple
CRP	C-reactive protein
CVD	Cardiovascular disease
eGFR	Estimated GFR
FPG	Fasting plasma glucose
GGT	γ-glutamyltransferase
HDL-C	High-density lipoprotein cholesterol
IDI	Integrated discrimination improvement
KIHD	Kuopio Ischaemic Heart Disease
NRI	Net reclassification improvement
SBP	Systolic blood pressure

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Introduction

Serum albumin, which is synthesised in the liver [1], is a useful marker of nutritional status and known to possess antioxidative properties [2, 3]. It is able to scavenge peroxy radicals [4] and inhibits copper-dependent lipid peroxidation systems [5]. Low serum albumin has been suggested to be an indicator of inflammation and liver disease [6, 7]. Serum albumin concentrations have also been demonstrated to be inversely correlated with several risk factors for diabetes such as age and BMI [1, 5, 8]. In addition to its physiological functions, a growing body of evidence indicates that serum concentrations of albumin may be associated with a wide range of disease outcomes including metabolic syndrome [9, 10], cardiovascular morbidity and mortality [6, 11, 12], cancer mortality [6] and all-cause mortality [11].

Emerging evidence indicates that serum albumin concentrations may be linked to type 2 diabetes risk. A limited number of prospective studies have been published reporting on the associations between baseline serum albumin concentrations and risk of type 2 diabetes [8, 13, 14], but their results have been inconsistent. Whereas some studies have shown inverse associations [13, 14], other studies have found no association between serum albumin and type 2 diabetes [8, 13], giving rise to uncertainty regarding the nature of the association. To help characterise and quantify more reliably the nature and magnitude of the association, we report a detailed assessment of the association of serum albumin concentration with incident type 2 diabetes in a population-based sample of 1,785 non-diabetic men from eastern Finland. In addition, we also report the extent to which serum albumin measurements could improve the prediction of type 2 diabetes in general population settings when added to a conventional risk prediction model.

Methods

Study population The study population consisted of a representative sample of men living in the city of Kuopio and its surrounding rural communities in eastern Finland. Subjects were participants in the Kuopio Ischaemic Heart Disease (KIHD) risk factor study, a longitudinal population-based study designed to investigate risk factors for cardiovascular disease (CVD), atherosclerosis and related outcomes [15]. Participants were 42–61 years of age during baseline examinations performed between March 1984 and December 1989. Of 3,433 potentially randomly eligible and randomly selected men, 2,682 (78%) volunteered to participate; 186 did not respond to the invitation and 367 declined to participate. Men with a prevalent self-reported history of diabetes, CVD, liver disease or kidney disease were excluded (n=198). Prevalent diabetes was defined as having a clinical diagnosis of diabetes and regular treatment with diet, oral hypoglycaemic agents or insulin therapy. The final cohort for the present analysis included 1,785 men with non-missing information on serum albumin and with established and emerging risk factors for type 2 diabetes. An incident case of type 2 diabetes was defined as a fasting plasma glucose (FPG) ≥7.0 mmol/l, a 2 h glucose tolerance test plasma glucose ≥11.1 mmol/l, or use of glucose-lowering medication according to self-report at re-examination 4, 11 and 20 years after baseline and by record linkage to the national hospital discharge registry and to the Social Insurance Institution of Finland register for reimbursement of medicine expenses. The Research Ethics Committee of the University of Eastern Finland approved the study, and each participant gave written informed consent.

Risk factor assessment Collection of blood specimens and the measurement of serum lipids, lipoproteins and glucose have been described previously [16]. Blood samples were taken between 08:00 and 10:00 hours. In addition to fasting, participants were instructed to abstain from drinking alcohol for at least 3 days and from smoking for at least 12 h prior to assessment. Measurement of serum albumin concentrations was made from frozen serum samples using Coulter's bromcresol purple (BCP) colorimetric assay (Kone Specific, Kone Corporation, Espoo, Finland). The serum samples were stored frozen at −80°C for 0.2–2.5 years. FPG was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany). Serum γ-glutamyltransferase (GGT) activity was measured using the kinetic method (Thermo Fisher Scientific, Vantaa, Finland) and C-reactive protein (CRP) with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Smoking, alcohol consumption and blood pressure were assessed as described previously [16]. BMI was computed as the ratio of weight in kilograms to the square of height in metres. Dietary energy intake was assessed by recording food intake over 4 days using a questionnaire, and caloric intake of nutrients was calculated using Nutrica software (version 2.5; National Public Health Institute, Turku, Finland) [17]. Physical activity was assessed using the KIHD 12 month leisure-time physical activity questionnaire [17, 18].

Statistical analyses Values of positively skewed variables (e.g. triacylglycerols, CRP and GGT) were natural log-transformed to achieve normality. We performed descriptive analyses summarising the baseline characteristics of the participants. We assessed potential associations of serum albumin concentrations with risk markers for type 2 diabetes using linear regression models. Time-to-event analyses were conducted using Cox proportional hazards models to examine the association of serum albumin with incident type 2 diabetes after confirming assumption of proportionality of hazards. The shape of the association with type 2 diabetes risk was

assessed by plotting HRs calculated within quartiles of baseline serum albumin concentration against the mean serum albumin concentration within each quartile. We used floating variances to calculate 95% CIs for the HR in each group, including the reference group, to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (bottom quartile) [19]. As the association showed an approximately linear shape, HRs were calculated per 1 SD higher serum albumin concentrations. The SD of the baseline serum albumin concentration was 3.6 g/l. HRs were adjusted for established type 2 diabetes risk factors (age, BMI, systolic blood pressure [SBP], smoking status, high-density lipoprotein cholesterol [HDL-C], physical activity, family history of diabetes and FPG) and further for $\log_e$ triacylglycerol, $\log_e$ CRP, $\log_e$ GGT, estimated GFR (eGFR), as calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [20], and total energy intake. We performed subgroup analyses using interaction tests to assess statistical evidence of any differences in HRs across levels of pre-specified individual level characteristics (such as age at survey, smoking status, BMI, SBP, FPG, HDL-C, eGFR and total energy intake). To avoid potential bias due to participants at high risk of diabetes or with underlying diabetes at baseline, we carried out additional analyses that excluded diabetes events ascertained in the first 5 years of follow-up.

To assess whether adding information on serum albumin values to conventional type 2 diabetes risk factors is associated with improvement in prediction of type 2 diabetes risk, we calculated measures of discrimination for censored time-to-event data (Harrell's C-index [21]) and reclassification [22, 23]. To investigate the change in C-index on the addition of serum albumin, two diabetes risk prediction models were fitted: the 9 year Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) risk model with several conventional risk factors (i.e. smoking, waist circumference and hypertension) [24], and the same model with the conventional risk factors plus serum albumin. We calculated the continuous net reclassification improvement (NRI) [23], a category-free version of the NRI, and the integrated discrimination improvement (IDI), which integrates the NRI over all possible cut-offs and is equivalent to the difference in discrimination slopes [22]. All statistical analyses were conducted using Stata version 12 (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics In the KIHD study, data were available for 1,785 participants with no known history of diabetes at baseline. The mean age of the participants was 53 (SD 5) years. Baseline descriptive characteristics of the participants are shown in Table 1. During an average follow-up of 20.4 years (36,640 person-years at risk), there were 382 incident type 2 diabetes events (annual rate 11.1/1,000 person-years at risk; 95% CI 10.1, 12.3). Serum albumin concentrations were weakly and positively correlated with physical measures (BMI and blood pressure) and with several lipid and metabolic markers. Weak inverse correlations were observed for age (r=−0.12), total cholesterol (r=−0.04), $\log_e$ CRP (r=−0.14) and $\log_e$ eGFR (r=−0.08). Baseline serum albumin concentrations were lower by 63% in current smokers compared with non-current smokers (Table 1).

Serum albumin concentrations and risk of incident type 2 diabetes In analyses adjusted for established type 2 diabetes risk factors (age, BMI, SBP, smoking status, HDL-C, physical activity, family history of diabetes and FPG), there was an approximately linear association between serum albumin and type 2 diabetes risk (Fig. 1). Statistical tests of the compatibility of the data with a linear vs a quadratic model suggested a better fit with a linear shape (p for linearity <0.05). The age-adjusted HR per 1 SD change in serum albumin concentration was 1.14 (95% CI 1.03, 1.27; p=0.013), which remained persistent (HR 1.15; 95% CI 1.03, 1.28; p=0.016) after further adjusting for established risk factors. The results remained consistent after additionally adjusting for $\log_e$ triacylglycerol, $\log_e$ CRP, $\log_e$ GGT, eGFR and total energy intake (HR 1.15; 95% CI 1.02, 1.29; p=0.018) (Table 2). HRs did not vary importantly in analyses that excluded diabetes events ascertained in the first 5 years of follow-up (data not shown). The associations did not vary significantly by levels of several clinically relevant characteristics and other risk markers (p for interaction >0.10 for each; Fig. 2).

Serum albumin concentration and type 2 diabetes risk prediction A diabetes risk prediction model containing conventional risk factors yielded a C-index of 0.7614 (95% CI 0.7130, 0.8098). After addition of information on albumin in the model, the C-index was 0.7740 (95% CI 0.7261, 0.8219), representing a non-significant increase of 0.0126 (95% CI −0.0055, 0.0306; p=0.17). The NRI and IDI were 15.8% (95% CI −5.1, 36.7; p=0.11) and −0.00002 (95% CI −0.0027, 0.0027; p=0.98), respectively (electronic supplementary material [ESM] Table 1).

Discussion

Our analyses of this population-based cohort of middle-aged men with over 20 years of follow-up and without a history of diabetes at baseline provide several relevant findings that have previously not been reported. There were weak associations of serum albumin concentrations with several established and

Table 1 Baseline participant characteristics and cross-sectional correlates of albumin

Characteristic	Mean (SD) or *n* (%)	Pearson correlation *r* (95% CI)[a]	Percentage difference (95% CI) in serum albumin concentration per 1 SD higher level of column 1 or compared with reference category in this column[b]
Serum albumin, g/l	42.3 (3.6)		
Questionnaire			
Age at survey, years	53 (5)	−0.12 (−0.16, −0.07)***	−34 (−44, −23)
Smoking status			
Non-smokers	1,237 (69.3)	–	Ref.
Current smokers	548 (30.7)	–	−63 (−74, −47)
Alcohol consumption, g/week	78.1 (146.1)	−0.03 (−0.07, 0.02)	−10 (−24, 6)
Total energy intake, kJ/day	2,511 (664)	−0.03 (−0.07, 0.02)	−10 (−23, 7)
Family history of diabetes			
No	1,300 (72.8)	–	Ref.
Yes	485 (27.2)	–	9 (−24, 57)
History of hypertension			
No	1,384 (77.5)	–	Ref.
Yes	401 (22.5)	–	4 (−30, 55)
Physical measurements			
BMI, kg/m^2	26.6 (3.4)	0.07 (0.03, 0.12)**	31 (11, 55)
Waist circumference, cm	90.6 (8.6)	0.02 (−0.02, 0.07)	8 (−8, 28)
SBP, mmHg	133.7 (16.5)	0.10 (0.06, 0.14)***	44 (22, 70)
DBP, mmHg	88.8 (10.5)	0.08 (0.04, 0.13)**	35 (15, 59)
Physical activity, kJ/day	1,516 (1,290)	0.01 (−0.04, 0.05)	3 (−12, 22)
Lipid markers			
Total cholesterol, mmol/l	5.88 (1.06)	−0.04 (−0.09, 0.00)	−14 (−27, 1)
LDL-C, mmol/l	4.02 (1.01)	−0.07 (−0.12, −0.03)*	−23 (−34, −9)
HDL-C, mmol/l	1.32 (0.30)	0.01 (−0.03, 0.06)	4 (−11, 23)
Log$_e$ triacylglycerol, mmol/l	0.08 (0.50)	0.11 (0.06, 0.15)***	47 (25, 73)
Metabolic and inflammatory markers			
Log$_e$ CRP, nmol/l	2.50 (0.96)	−0.14 (−0.18, −0.10)***	−40 (−49, −29)
FPG, mmol/l	5.19 (0.80)	0.00 (−0.04, 0.05)	2 (−14, 20)
Log$_e$ GGT, μkat/l	−1.00 (0.64)	0.08 (0.03, 0.13)**	33 (13, 57)
eGFR, ml min^{-1} 1.73 m^{-2}	87.5 (17.3)	−0.08 (−0.12, −0.03)**	−24 (−36, −11)

Complete baseline information was available on 1,785 individuals (382 with type 2 diabetes) without prevalent diabetes, cardiovascular disease or liver disease and with no missing information on serum albumin, age, BMI, SBP, smoking, HDL-C, physical activity, family history of type 2 diabetes, FPG, triacylglycerol, CRP, GGT, eGFR and total energy intake

[a] Pearson correlation coefficients between serum albumin and the row variables

[b] Percentage change in serum albumin concentration per 1 SD increase in the row variable (or, for categorical variables, the percentage difference in mean serum albumin concentration for the category vs the reference) adjusted for age

*p<0.05; **p<0.01; ***p<0.001

DBP, diastolic blood pressure; LDL-C, LDL-cholesterol; Ref., reference

emerging diabetes risk factors. Our data also suggest that baseline serum albumin concentration is positively and independently associated with incident type 2 diabetes in an approximately linear fashion. In addition, these findings remained generally consistent across several clinically relevant subgroups and at different levels of risk factors. The associations remained similar in analyses that excluded diabetes events ascertained in the first 5 years of follow-up.

Our finding of a positive association between serum albumin and type 2 diabetes is in contrast to the limited previous reports on an association (ESM Table 2). Abbasi and colleagues found no significant association in one of their cohorts of men and women aged 28–75 years [13]. In the Atherosclerosis Risk in Communities study [8], low serum albumin was associated with an increased risk of type 2 diabetes among men and women aged 45–65 years in analyses

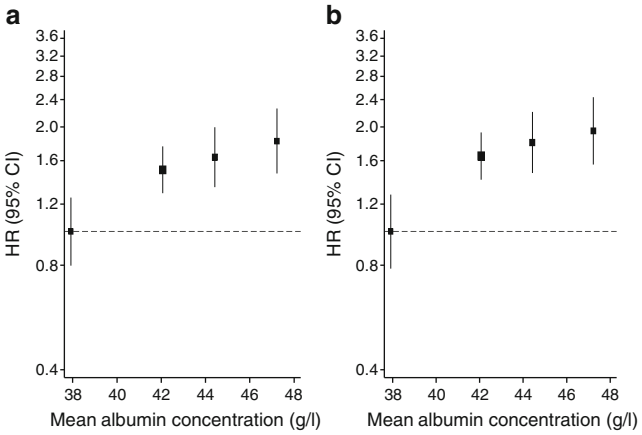

Fig. 1 HRs (95% CI) for incident type 2 diabetes by quartiles of baseline concentrations of serum albumin, plotted on a logarithmic scale: (**a**) adjusted for age; (**b**) adjusted for age, BMI, SBP, smoking, HDL-C, physical activity, family history of type 2 diabetes and FPG. The figure shows the HR and 95% 'floating absolute' CIs per quartile of serum albumin concentrations. The size of the box is proportional to the inverse of the variance of HR. Note: the first category is the reference

adjusted for several conventional risk factors; however, the association became non-significant on further adjustment for BMI and waist/hip ratio. In the 6 year longitudinal investigation of the Western New York Study, in which only 61 people met the case definition of incident type 2 diabetes [14], Stranges and colleagues reported a decreased risk of type 2 diabetes incidence with high (upper tertile) serum albumin concentrations. Similar to the finding of an inverse association between serum albumin concentration and type 2 diabetes in previous studies, other studies have demonstrated associations between serum albumin concentrations and outcomes such as cardiovascular disease [6, 11, 12], cancer mortality [6] and all-cause mortality [11]. Our findings of a positive association are at odds with previous findings. As to whether these previous observations reflect true associations remains unclear. Several reasons, however, could explain the conflicting results. First, previous studies were limited by the following: (1) inadequate power because of small sample sizes; (2) short follow-up durations; and (3) inability to fully examine the impact of adjustment for potential confounding. Second, there may be true differences, due to differences in study population characteristics such as age, sex, race or genetic background. Third, these differences may also be related to differences in the type of blood samples (serum or plasma) used for albumin measurements, assay methods for serum albumin, ascertainment and case definition of type 2 diabetes outcomes or a combination of all of these (ESM Table 2). Three out of all four previous studies employed the use of a bromcresol green (BCG) dye-binding assay, which is subject to non-specific interference from binding to non-albumin proteins and may overestimate the associations [25]. We, however, used the BCP assay, which agrees more closely with the gold standard of immunonephelometry [25]. Fourth, there are suggestions that low serum albumin concentrations may be an indicator of underlying subclinical disease (such as renal or liver disease, malnutrition and anaemia) [11, 14], which may produce spurious inverse associations with type 2 diabetes and other chronic conditions [26].

The current study differs in several important ways from previous studies, which enhances the reliability of the findings: (1) the analysis was based on a large dataset with adequate power to demonstrate the observed associations; (2) participants were selected from a nationally representative sample, with a high response rate; they were prospectively followed for an average period of 20 years and there was no loss to follow-up; (3) there was information on a comprehensive panel of lifestyle and biological markers to allow adequate adjustment for potential confounding; and (4) individuals with prevalent diabetes, CVD, liver disease or renal disease were excluded from the analyses; in addition, a sensitivity analysis excluded diabetes events in the first 5 years of follow-up, thus minimising the effects of any pre-existing disease on serum albumin concentrations ('reverse causation') and therefore more closely reflecting a causal association. In addition, given that several previous studies have demonstrated positive associations between serum albumin and the metabolic syndrome [9, 10] (a known risk factor for type 2 diabetes [27, 28]), it is possible that our findings may reflect true associations. Nonetheless, collaborative pooling of individual participant data from large-scale prospective studies with long follow-up durations may be needed to clarify the associations.

The mechanistic pathways for the link between elevated serum albumin and the development of type 2 diabetes are unclear, although a higher dietary protein intake has been

Table 2 HRs (95% CI) for incident type 2 diabetes per 1 SD higher baseline concentration of serum albumin

Serum albumin, g/l	Events/total, *n*	Model 1		Model 2		Model 3	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Per 1 SD increase	382/1,785	1.14 (1.03, 1.27)	0.013	1.15 (1.03, 1.28)	0.016	1.15 (1.02, 1.29)	0.018

Model 1, adjusted for age

Model 2, model 1 plus BMI, SBP, smoking, HDL-C, physical activity, family history of type 2 diabetes and FPG

Model 3, model 2 plus triacylglycerol, CRP, GGT, eGFR and total energy intake

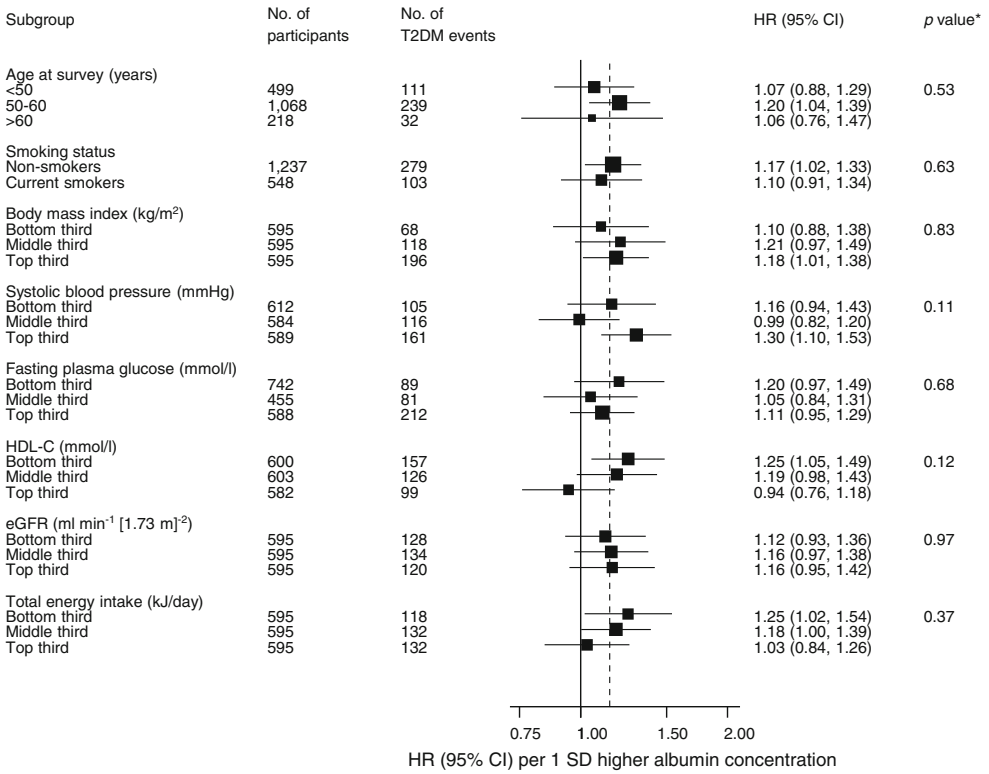

Fig. 2 HRs (95% CI) for incident type 2 diabetes (T2DM) risk per 1 SD higher baseline concentration of serum albumin in subgroups of participants, plotted on a logarithmic scale. The figure shows the *p* values for interaction

suggested for the positive association between serum albumin and the metabolic syndrome [10]. Our findings did not suggest any evidence of effect modification by total dietary energy intake. If our findings of an independent and linear association between serum albumin and type 2 diabetes risk reflect a true association, it may have implications for the prevention of type 2 diabetes. Although several risk scores incorporating established risk factors for diabetes exist [29–31], their clinical utility has been questioned, as the identification of individuals at increased risk remains a difficult undertaking [32]. There is therefore stimulated interest in evaluating the relevance of additional risk factors. Serum albumin has been suggested as an emerging risk factor that may add to the identification of future diabetic patients beyond that of traditional risk factors [14]. Due to its limited and weak correlation with established risk factors, there is a potential for serum albumin to improve risk prediction over and above these established risk factors [32]. Although our results showed a graded increase in type 2 diabetes risk with increasing serum albumin concentrations, additional information on serum albumin provided no significant improvement in type 2 diabetes risk discrimination. Given that serum albumin is a simple, standardised, cost-effective and scalable biomarker, we propose additional larger studies and formal risk analyses (such as those conducted by our group [33, 34]) to assess its role in type 2 diabetes risk prediction.

In addition to the several strengths enumerated above, our study did have some limitations. The study included only men and the findings cannot necessarily be generalised to women. Although we accounted for many potential confounders including key clinical characteristics, liver and kidney function, and caloric intake, there was a potential for residual confounding, as with all observational studies. Furthermore, we could not correct for within-individual variation in serum albumin concentrations over time, which may have underestimated the associations demonstrated, as we had only a one-time measurement of serum albumin. Though there are suggestions that serum albumin exhibits low within-individual variation (the correlation coefficient between measured levels of serum albumin several years apart has been reported to be approximately 0.70 [1]), studies with repeat measurements of serum albumin are still needed to assess its variability in greater detail.

In summary, there is an approximately linear positive association between serum albumin concentration and incident type 2 diabetes risk, which is independent of established risk factors. However, no improvement in diabetes risk prediction was demonstrated. Further studies are needed to determine whether this relationship represents a causal association.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement SKK, HK and JAL participated in the conception and design of the study. SKK analysed the data. SKK, HK and JAL were involved in interpretation of data, and contributed to drafting the manuscript and revising it critically for important intellectual content. All authors approved the manuscript for submission. JAL supervised the study and is the guarantor of this work.

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