

**Serum albumin, cardiometabolic and other adverse outcomes: systematic review and meta-analyses of 48 published observational cohort studies involving 1,492,237 participants**

Samuel Seidu<sup>a,b,\*</sup>, Setor K Kunutsor<sup>c,d</sup>, Kamlesh Khunti<sup>a,b</sup>

<sup>a</sup>Leicester Diabetes Centre, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4WP, UK <sup>2</sup>Diabetes

<sup>b</sup>Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4WP, UK

<sup>c</sup>National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK

<sup>d</sup>Musculoskeletal Research Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK

**\*Corresponding author:**

Samuel Seidu, Leicester Diabetes Centre, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4WP, UK; Email: [sis11@leicester.ac.uk](mailto:sis11@leicester.ac.uk)

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## **ABSTRACT**

*Objectives.* A general body of evidence suggests that low serum albumin might be associated with increased risk of adverse cardiometabolic outcomes, but findings are divergent. We aimed to quantify associations of serum albumin with the risk of type 2 diabetes (T2D), cardiovascular disease (CVD), all-cause mortality, and other adverse outcomes using a systematic review and meta-analyses of published observational cohort studies. *Design.* MEDLINE, Embase, Web of Science, and manual search of relevant bibliographies were systematically searched to January 2020. Relative risks (RRs) with 95% confidence intervals (CIs) comparing top versus bottom thirds of serum albumin levels were pooled. *Results.* Fifty-four articles based on 48 unique observational cohort studies comprising of 1,492,237 participants were eligible. Multivariable adjusted RRs (95% CIs) comparing the top vs bottom third of serum albumin levels were: 1.03 (0.86-1.22) for T2D; 0.60 (0.53-0.67) for CVD; 0.74 (0.66-0.84) for coronary heart disease (CHD); 0.57 (0.36-0.91) for CHD death; 0.76 (0.65-0.87) for myocardial infarction; 0.66 (0.55-0.77) for all-cause mortality; 0.71 (0.61-0.83) for venous thromboembolism; 0.65 (0.48-0.88) for cancer mortality; and 0.62 (0.46-0.84) for fracture. Heterogeneity between contributing studies of T2D was partly explained by sample sizes of studies ( $p$  for meta-regression=0.035). *Conclusions.* Elevated levels of serum albumin are associated with reduced risk of vascular outcomes, all-cause mortality, certain cancers, and fracture. Inconsistent findings for T2D may be attributed to selective reporting by studies. Further research is needed to assess any potential causal relevance to these findings and the role of serum albumin concentrations in disease prevention.

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## **KEYWORDS**

serum albumin; cardiovascular disease; type 2 diabetes; metabolic syndrome; cohort study; systematic review; meta-analysis

## **Introduction**

Serum albumin, a protein which is synthesized in the liver,[1] is a historical marker of nutritional status.[2] Serum albumin has antioxidative properties[3] and low serum concentrations have been suggested to be an indicator of inflammation, hypercoagulable states and liver disease.[4, 5] Serum albumin concentrations have been demonstrated to be inversely correlated with several risk factors for cardiometabolic disease such as age, total cholesterol, body mass index (BMI), and inflammatory markers.[6, 7, 8] Evidence suggests that serum albumin concentrations may be associated with a wide range of cardiometabolic outcomes including cardiovascular disease (CVD),[4, 9, 10] type 2 diabetes,[11, 12] metabolic syndrome,[13, 14], and all-cause mortality.[9] Though the general body of evidence suggests low serum albumin is associated with increased risk of these adverse outcomes; some of the findings have not been consistent. For example, on the relationship between serum albumin and type 2 diabetes; whereas some studies have demonstrated inverse associations,[11, 12] others have reported positive associations,[15] and some others have found no associations.[8, 12] Several reasons could explain the conflicting results and could be related to study design factors such as small sample sizes (low event rates).[15] Furthermore, some previous studies were based on cross-sectional designs,[13, 14] hence the temporal nature of the associations is limited. Though established risk factors explain a large proportion of the risk for these adverse cardiometabolic outcomes, their pathogeneses are still not fully established as it appears other additional factors may be involved. There is therefore a priority to identify and evaluate potentially modifiable risk factors that may have predictive or causal relevance, to help tailor preventive and therapeutic strategies for these conditions. Serum albumin is such a biomarker which has potential promise for the prevention of adverse cardiometabolic outcomes. Given that individual studies are often poorly powered and their results are not always definitive, we sought to quantify the nature, magnitude and specificity of potential longitudinal associations of serum albumin with the risk of adverse cardiometabolic outcomes such as type 2 diabetes, CVD, metabolic syndrome, and all-cause mortality in more detail than ever before using a systematic review and meta-analysis of available observational cohort studies. In subsidiary analyses, we also explored associations with other adverse health outcomes such as venous thromboembolism (VTE), cancer, and fracture outcomes.

## **Methods**

### ***Data sources, searches and screening***

This review has been registered in the PROSPERO prospective register of systematic reviews (CRD42019125869). The systematic review and meta-analysis was based on a predefined protocol and conducted in accordance with PRISMA and MOOSE guidelines [16, 17] (**Supplementary Tables 1-2**). MEDLINE and Embase were searched from inception to 30 January 2020. The computer-based searches used a combination of MeSH terms related to the exposure (e.g., serum albumin) and outcomes (e.g., cardiovascular disease, type 2 diabetes, mortality) in humans with no language restrictions. The detailed search strategy is reported in **Supplementary Table 3**. The titles and abstracts of citations identified from the databases were then initially screened to identify articles potentially eligible for inclusion. Following this, full texts of relevant articles were acquired for further evaluation. The full text evaluation was independently conducted by two authors (SKK and SS) based on the inclusion criteria indicated below. Any disagreements regarding eligibility of an article was discussed, with involvement of a third author when necessary (KK). Reference lists of relevant studies and the “cited by” function in Web of Science were assessed to identify additional studies missed by the search strategy.

### ***Eligibility criteria***

Studies were included if they met the following search criteria: were population-based observational (prospective or retrospective cohort, case cohort, or nested case-control) in design; had sampled from healthy (i.e., were based on initially healthy participants) or general populations (ie, populations with both healthy and prevalent cases of cardiometabolic disease at baseline); had evaluated the associations of circulating albumin concentrations with primary and secondary outcomes; and had at least one year of follow-up. The primary outcomes were cardiometabolic outcomes and included CVD (including cardiovascular endpoints such as coronary heart disease (CHD), myocardial infarction (MI), and stroke), type 2 diabetes, metabolic syndrome, and all-cause mortality. Secondary outcomes were other cardiometabolic and nonvascular outcomes including hypertension, heart failure, venous thromboembolism, dementia, cancer and fracture. We excluded studies for the following reasons: (i) they only reported on mean levels and standard deviations of serum albumin in cases

and non-cases; (ii) were based exclusively in participants with pre-existing cardiometabolic disease; or (iii) were case-control, cross-sectional or ecological in design.

### ***Data extraction and quality assessment***

One author (SKK) initially extracted data from eligible studies using a standardized predesigned data collection form, which has been used in previous similar reviews.[18, 19] A second author (SS) independently checked the extracted data with that in original articles. Data were extracted for the following study characteristics: author and year of publication, country of study, baseline year of study, study design, age, sex, assay type, type of outcome, sample size and number of outcomes, duration of follow-up, degree of adjustment for potential confounders [defined as ‘+’ (when risk estimates were adjusted for age and/or sex); ‘++’ (further adjustment for established risk factors such as smoking status, body mass index, blood pressure, lipids); and ‘+++’ (additional adjustment for emerging risk factors such as inflammatory markers)], and risk estimates reported for greatest adjustment for potential confounders. To avoid double counting of participants within a study cohort, study selection was limited to a single set of comprehensive information when there were several publications involving the same study cohort. Selection was based on the study with the most up-to-date information (longest follow-up duration and/or analysis covering the largest number of participants). Methodological quality of studies was assessed using the nine-star Newcastle–Ottawa Scale (NOS),[20] which uses pre-defined criteria namely: selection (population representativeness), comparability (adjustment for confounders), and ascertainment of outcome. Nine points on the NOS reflects the highest study quality.

### ***Data synthesis and analysis***

Summary measures of associations were presented as relative risks (RRs) with 95% confidence intervals (CIs). To enable consistency in the pooling approach and enhance interpretation of the findings, RR estimates for the associations of serum albumin and outcomes were transformed to consistently correspond to the comparison of the top versus bottom third of the distribution of serum albumin levels in each study, using standard statistical methods previously described [19, 21] (**Supplementary Table 4**). Briefly, log risk estimates were transformed assuming a normal distribution (or that a transformation of the exposure variable

for which the risk ratio is based was normally distributed), with the comparison between top and bottom thirds being equivalent to 2.18 times the log risk ratio for a 1 standard deviation increase (or equivalently, as 2.18/2.54 times the log risk ratio for a comparison of extreme quarters and as 2.18/2.80 times the log risk ratio for a comparison of extreme quintiles). Standard errors of the log risk estimates were calculated using reported confidence intervals and were standardised in the same way. For estimates that could not be transformed, the top versus bottom categories were used as reported in the included studies. We have shown that pooled estimates from transformed and untransformed data are qualitatively similar.[22] When the highest quantile (eg, top third) was used as the referent, we converted the reported risk estimate into its reciprocal. When studies reported more than one estimate of an association according to subgroups (e.g., by sex), a within-study summary estimate was calculated using a fixed effect meta-analysis. Random-effects models were used to combine RRs to account for the effect of heterogeneity.[23] Heterogeneity between studies was assessed using the standard  $\chi^2$  statistic and the  $I^2$  statistic.[24] We assessed heterogeneity between cohorts by comparing results from studies grouped according to prespecified study level characteristics such as geographical location, sex, average age at baseline, average duration of follow-up, number of outcomes recorded, degree of statistical adjustment, and study quality using random effects meta-regression.[25] We assessed for evidence of publication bias using visual inspection of Begg's funnel plots[26] and Egger's regression symmetry tests.[27] All analyses were conducted using Stata MP 16 (Stata Corp, College Station, Texas, USA).

## **Results**

### ***Study identification and selection***

The study selection process is illustrated in **Figure 1**. The initial search as well as the manual screening of relevant citations identified 2,886 potentially relevant citations. After screening of citations based on titles and abstracts, 77 citations were selected for full text evaluation. A total of 23 articles were excluded because (i) exposure was not relevant (n=11); (ii) study design not relevant (n=4); (iii) duplicate of a previous publication using the same cohort (n=4); (iv) outcome not relevant (n=3); and (v) risk estimates could not be calculated (n=1). In total, we included 54 articles based on 48 unique observational cohort studies.[5, 6, 8, 9, 10, 11, 12,

15, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73]

### *Study characteristics and quality*

**Table 1** summarizes characteristics and quality assessment scores of each of the eligible studies evaluating the associations between serum albumin and risk of several outcomes. Publication dates of eligible studies ranged from 1990 to 2020. Overall, the 48 unique cohorts comprised of 1,492,237 participants. The majority of studies were based on prospective cohort designs (n=37), with the remainder based on retrospective cohort (n=4), nested case-control (n=4), and case-cohort (n=3) designs. Overall, 19 studies were conducted in North America (USA), 17 in Europe (Austria, Finland, France, Germany, Netherlands, Norway, Russia, Spain, Sweden, and UK), and 12 in Asia (China, Japan, Korea, and Taiwan). Overall, the average baseline age of participants in the included studies ranged from 37.6 to 97.0 years and the weighted mean age was 50.9 years. The average overall duration of follow-up for outcomes ranged from 1.0 to 28.5 years, with a weighted mean follow-up duration of 8.8 years. For studies providing these data, the overall average serum albumin level ranged from 37.3 to 51.0 g/l with a weighted mean of 42.7 g/l. The overall methodological quality scores of studies using NOS ranged from 5 to 9.

### *Serum albumin and risk of primary outcomes*

**Figure 2** provides a summary of meta-analyses of the associations between serum albumin and risk of the primary and secondary outcomes evaluated. In meta-analysis of 9 studies,[8, 11, 12, 15, 54, 66, 68, 73] comparing the top versus bottom third of serum albumin levels, the pooled fully-adjusted RR (95% CI) of type 2 diabetes was 1.03 (0.86-1.22) (**Figure 3**). There was significant heterogeneity between contributing studies ( $I_2 = 68\%$ ; 95% CI 33, 85%;  $p$  for heterogeneity < 0.001), which seemed to be partly explained by the sample size ( $p$  for meta-regression = 0.04). Smaller studies were more likely to report more extreme results compared with larger studies (**Supplementary Figure 1**). In meta-analyses of cardiovascular outcomes, RRs (95% CIs) were 0.60 (0.53-0.67;  $I_2 = 22\%$ ; 95% CI 0, 66%;  $p$  for heterogeneity = 0.27, n=6 studies[38, 42, 52, 62, 71, 74]) for CVD; 0.74 (0.66-0.84;  $I_2 = 59\%$ ; 95% CI 5, 82%;  $p$  for heterogeneity = 0.02, n=7 studies[10,

30, 35, 38, 42, 69, 74) for CHD; 0.57 (0.36-0.91;  $I_2 = 51\%$ ; 95% CI 0, 86%;  $p$  for heterogeneity=0.13,  $n=3$  studies[30, 35, 38]) for CHD mortality; 0.76 (0.65-0.87;  $I_2 = 0\%$ ; 95% CI 0, 85%;  $p$  for heterogeneity =0.59,  $n=4$  studies[9, 30, 48, 58]) for MI; and 0.99 (0.60-1.63;  $I_2 = 91\%$ ; 95% CI 75, 96%;  $p$  for heterogeneity<0.001,  $n=3$  studies[33, 42, 58]) for stroke comparing top versus bottom thirds of serum albumin levels (**Figure 2; Supplementary Figure 2**). Comparing the top versus bottom thirds of serum albumin levels in 21 studies, the pooled RR (95% CI) for all-cause mortality was 0.65 (0.55-0.77) with substantial heterogeneity between contributing studies ( $I_2 = 97\%$ ; 95% CI 96, 97%;  $p$  for heterogeneity<0.001) (**Figure 4**), which seemed to be explained partly by the duration of follow-up ( $p$  for meta-regression=0.023). The association was stronger for studies with shorter follow-up duration (<10 years) compared with studies of longer follow-up duration ( $\geq 10$  years) (**Supplementary Figure 3**). In meta-analysis of 3 studies that compared hypoalbuminaemia versus normal albumin,[37, 43, 50] the RR (95% CI) for all-cause mortality was 1.31 (0.86-1.98;  $I_2 = 67\%$ ; 95% CI 0, 91%;  $p$  for heterogeneity=0.05) (**Supplementary Figure 4**). Results from single reports showed a decreased risk of ischaemic stroke,[58] SCD,[48] and non-SCD[48] comparing the top versus bottom tertile of serum albumin levels; whereas the risk of MetS[60] and stroke mortality[33] was increased (**Supplementary Figure 5**). Three studies could not be included in the pooled analyses due to the inconsistent reporting of and lack of complete data on risk estimates.[29, 45, 64] Darne et al.[29] in their report published in 1990, showed that serum albumin was not significantly associated with cardiovascular, cancer, and all-cause mortality. In the prospective study of the associations of biomarkers of inflammation and malnutrition with the risk of death in health elderly people, Carriere and colleagues showed that low serum albumin was associated with early death in men; no associations were demonstrated for women.[45] In patients without pre-existing cardiovascular diagnoses, Hayward and colleagues demonstrated low serum albumin to be associated with an increased risk of cardiac events.[64]

### ***Serum albumin and risk of secondary outcomes***

In meta-analysis of 4 studies,[5, 6, 57] comparing the top versus bottom third of serum albumin levels, the pooled RR (95% CI) of VTE was 0.71 (0.61-0.83;  $I_2 = 0\%$ ; 95% CI 0, 85%;  $p$  for heterogeneity=0.41) (**Figure 2; Supplementary Figure 6**). In meta-analyses of cancer endpoints, RRs (95% CIs) were 0.65 (0.48-0.88,  $I_2$

=79%; 95% CI 44, 92%; *p* for heterogeneity=0.003, n=4 studies[42, 62, 65, 71]) for cancer mortality and 0.92 (0.85-1.00,  $I^2$ =0%; 95% CI 0, 0%; *p* for heterogeneity=0.76, n=3 studies[39, 63, 65]) for colorectal cancer comparing top versus bottom thirds of serum albumin (**Supplementary Figure 7**). The corresponding RR (95% CI) for fracture in meta-analysis of two studies[36, 72] was 0.62 (0.46-0.84) (**Supplementary Figure 8**). Findings from single reports showed a decreased risk of heart failure,[49] hypertension,[56] breast cancer,[65] colorectal cancer death,[63] and colon cancer;[34] an increased risk of ovarian cancer[67] and no significant associations with all-cause cancer,[38] lung cancer,[65] and prostate cancer[65] (**Supplementary Figure 8**). In single studies that compared hypoalbuminaemia with normal albumin levels, the risk was increased for heart failure,[50] cancer,[61] and mild cognitive impairment[70] (**Supplementary Figure 9**).

### ***Publication bias***

Though tests of publication bias have low power and are unreliable in meta-analysis involving <10 studies,[75] we assessed for publication bias among studies of type 2 diabetes as the results of the subgroup analysis suggested evidence of selective reporting (small study effects) (**Supplementary Figure 1**). There was no evidence of publication bias across studies of type 2 diabetes, with the funnel plot showing no evidence of asymmetry (**Supplementary Figure 10**) and Egger's test for bias giving a *p*-value of 0.72. A funnel plot of the 21 studies reporting on the associations between serum albumin and all-cause mortality risk showed visual evidence of symmetry (**Supplementary Figure 10**) which was consistent with Egger's regression symmetry test (*p*=0.34). We also found no evidence of such selective reporting when studies were grouped by sample size in meta-regression analysis (i.e., results were similar for smaller and larger studies) (**Supplementary Figure 3**).

## **Discussion**

### ***Key findings***

These meta-analyses on the associations between serum albumin and several adverse outcomes indicates that elevated circulating levels of serum albumin in approximately healthy people are associated with reduced risk of CVD endpoints (including composite CVD, CHD, MI, SCD, and heart failure), all-cause mortality,

hypertension, VTE, cancer mortality, breast cancer, colon cancer, colorectal cancer, and fracture. The risk was however increased for MetS and ovarian cancer. There were no significant associations with type 2 diabetes, lung cancer, and prostate cancer. The association of serum albumin with type 2 diabetes seemed to be modified by sample size; smaller studies were more likely to report more extreme results compared with larger studies, though the associations were not significant. Furthermore, our findings suggested that the association between serum albumin and all-cause mortality risk may be modified by the duration of follow-up, with stronger associations being observed for shorter follow-up durations.

### ***Comparison with previous work***

In a previous meta-analysis published over two decades ago, Danesh and colleagues demonstrated low levels of serum albumin to be associated with increased risk of CHD in pooled analysis of eight studies. To our knowledge, this review represents the first comprehensive evaluation of aggregate observational cohort data on the associations of serum albumin with several cardiometabolic and other adverse health outcomes. Being the first attempt at doing this, these findings cannot directly be compared to previous work. Though generally mounting evidence has suggested that low levels of serum albumin are associated with increased risk of cardiometabolic outcomes such as type 2 diabetes, MetS, and CVD (and vice versa), the evidence has been inconsistent in the absence of meta-analyses of the existing data. The current study therefore establishes robust observational associations of serum albumin with the risk of several adverse outcomes.

### ***Possible explanations for findings***

Several plausible biological pathways might underlie some of the associations demonstrated. It is well established that inflammatory processes are involved in the aetiopathogenesis of vascular disease.[76, 77] Indeed, several “downstream” and “upstream” markers of inflammation such as C-reactive protein (CRP), fibrinogen, interleukins, and tumour necrosis factor alpha (TNF- $\alpha$ ) have been demonstrated to be associated with the risk of CHD.[78, 79, 80] Serum albumin is a negative acute phase reactant and is synthesized by the liver. In the presence of systemic inflammation, there is hepatic synthesis of other acute-phase proteins rather than serum albumin.[81] Hence, it has been suggested that low serum albumin levels may reflect

inflammatory states,[5] which underlie the pathogenesis of vascular disease. Since an inflammatory hypothesis has also been postulated in the development of VTE[82] and other outcomes such as all-cause mortality, hypertension, cancer, and fracture,[83] these same inflammatory processes may explain the observational relationships observed. However, since some of the observed associations between serum albumin and outcomes were independent of inflammatory markers such as CRP, interleukins, and TNF- $\alpha$ , it is likely that other pathways may be involved apart from inflammation. Low serum albumin may be a marker of a hypercoagulable state[5] and an indicator of health conditions such as liver disease, nephrotic syndrome, and malignancy, which increase the risk of VTE.[84, 85, 86, 87] Low serum albumin is also an indicator of poor nutrition,[2] functional decline,[88, 89, 90] and frailty,[37, 91] which all predispose to an increased risk of fractures. Oxidative stress, insulin resistance, and endothelial dysfunction in addition to inflammation, have been implicated in the development of hypertension; [92, 93] serum albumin has antioxidant properties[94] and also inhibits endothelial apoptosis,[95] hence high levels of serum albumin may protect against the development of hypertension. The potent antioxidant activity of serum albumin may contribute to its protective role on cancer risk. There were differential effects of albumin levels on the risk of site-specific cancers, which may reflect the fact that different types of cancer do not have the same pathogenic process. Whether higher serum albumin predisposes to an increased risk of MetS and ovarian cancer or is a marker of these adverse outcomes is unclear. The increased risk of ovarian cancer associated with increased serum albumin is unexpected given that ovarian cancer is associated with low serum albumin levels.[96] Schwartz and colleagues[67] speculate that elevated serum albumin could increase ovarian cancer risk by delivering higher levels of hormones to ovarian tissue, since steroid hormones in blood are bound to albumin. The authors also report that these findings may reflect increased albumin synthesis by ovarian cells.[67] With the inconsistent findings reported for the association between serum albumin and type 2 diabetes in individual studies, pooled analysis showed no evidence of an association. These findings were unexpected given the plausible pathways underlying the associations between serum albumin and adverse cardiometabolic outcomes, which suggest that serum albumin might reduce the risk of type 2 diabetes. Indeed, two of the included studies evaluated the associations between serum albumin change during follow-up and type 2 diabetes risk and observed that an increase in serum albumin during follow-up reduces the risk of type 2

diabetes.[68, 73] Though there was no evidence of publication bias using formal tests, subgroup analyses suggested the current findings might be due to selective reporting of studies (small study effects). It is well established that due to ageing, changes in lifestyle, chronic disease, and errors in exposure assessments, using baseline measurements of an exposure could underestimate the true strength of an association between an exposure and disease outcome due to the phenomenon of regression dilution bias.[97] Since our analyses were based on baseline serum albumin concentrations, the pooled estimates could be underestimates. In addition, given the substantial heterogeneity between contributing studies for type 2 diabetes which may be explained by factors such as differences in population characteristics (race, sex, genetic background, and underlying subclinical disease) and study design characteristics (blood sampling, assays for serum albumin measurement, or confounder adjustment), these findings need careful interpretation and replication in future studies. Finally, evidence of effect modification by follow-up duration on the serum albumin-mortality association might reflect protein degradation between sample collection and assay measurements for serum albumin. Serum samples for determination of albumin were stored at low temperatures (-20°C or less) for several years by some of the studies and this could have affected the recovery rates of albumin.

### ***Implications of findings***

Although the associations demonstrated do not establish causality for any of the outcomes assessed, the comprehensive evaluation helps to bridge the gaps in translating basic scientific findings into clinical practice. Serum albumin is a simple, standardised, cost-effective and scalable biomarker which may represent a potential therapeutic target for the prevention of adverse cardiometabolic outcomes – increasing or avoiding low serum albumin levels could be a strategy for reducing the risk of these health outcomes. A number of randomized controlled trials in surgery have demonstrated that nutritional supplementation is associated with reduced risk of complications such as fracture.[98, 99] Studies are needed to ascertain if the current findings have any causal relevance (Mendelian randomization) and definitive trials are also needed to investigate potential therapeutic implications of albumin supplementation.

### ***Strengths and limitations***

This study has several strengths. This represents the first attempt at summarising the overall evidence on the associations of serum albumin with multiple outcomes using meta-analyses. We only included studies that had exclusively recruited participants from general populations, thereby potentially minimizing any ‘reverse-causation’ effects of clinically evident pre-existing disease on serum albumin levels. Though there was inconsistent reporting of risk comparisons by included studies, we were able to standardise and harmonise risk estimates to a common scale (extreme tertiles) to ensure consistency in the pooling approach. Other strengths included assessment of exploration of heterogeneity and evaluation for publication bias where possible. Our review also had potential limitations. First, some of the findings were based on single or limited number of reports and hence require replication in future studies. Second, we were unable to perform consistent multivariate adjustments by combining models with the same set of potential confounders owing to the reliance on published data with variable degrees of adjustments across eligible studies. Third, we were unable to correct the estimates for within-person variation in serum albumin levels over time which may have underestimated associations, because the majority of studies evaluated associations using baseline levels of serum albumin. It has been reported that serum albumin may exhibit low within-individual variation (the correlation coefficient between measured levels of serum albumin several years apart is approximately 0.70 [1]); however, studies with repeat assessments of serum albumin are still needed to assess its variability in greater detail. Fourth, given the substantial heterogeneity between contributing studies for some of the outcomes (type 2 diabetes and all-cause mortality), it was arguable whether a summary risk estimate should be presented rather than reporting estimates in relevant subgroups. The presence of substantial heterogeneity makes pooling of risk estimates somewhat controversial; however, in addition to the summary risk estimate, we have also reported risk estimates for the several subgroups assessed although little of the heterogeneity was explained by any of these study characteristics.

### **Conclusion**

This aggregate systematic review and meta-analyses of long-term observational cohort studies involving apparently healthy adults shows that elevated levels of circulating serum albumin are associated with reduced

risk of vascular disease, all-cause mortality, hypertension, VTE, certain cancers, and fracture. Inconsistent findings for type 2 diabetes may be attributed to selective reporting by studies. Further research is needed to assess any potential causal relevance to some of these findings and the role of serum albumin concentrations in disease prevention.

### **Disclosure statement**

No potential conflict of interest was reported by the authors.

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## **Figure legends**

**Figure 1.** PRISMA flow diagram

**Figure 2.** Summary associations of serum albumin with primary and secondary outcomes

CHD, coronary heart disease; CI, confidence interval (bars); CVD, cardiovascular heart disease; MI, myocardial infarction; RR, relative risk; SCD, sudden cardiac death; VTE, venous thromboembolism

**Figure 3.** Associations of serum albumin with type 2 diabetes risk in eligible studies

The summary estimates presented were calculated using random effects models; CI, confidence interval (bars); RR, relative risk; T2D, type 2 diabetes

**Figure 4.** Associations of serum albumin with all-cause mortality risk in eligible studies

The summary estimates presented were calculated using random effects models; CI, confidence interval (bars); RR, relative risk